PDR®

51 EDITION

1997

PHYSICIANS' DESK REFERENCE®

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PRECAUTIONS

GENERAL

Patients should be adequately hydrated prior to the infusion and blood pressure should be monitored during the infusion. ETHYOL should be administered as a 15-minute infusion (See DOSAGE and ADMINISTRATION).

The safety of ETHYOL administration has not been established in elderly patients, or patients with preexisting cardiovascular or cerebrovascular conditions such as ischemic heart disease, arrhythmias, congestive heart failure, or history of stroke or transient ischemic attacks. ETHYOL should be used with particular care in these and other patients in whom the common ETHYOL adverse effects of nausea/vomiting and hypotension may be more likely to have serious consequences.

Drug Interactions

There are no known drug interactions with ETHYOL. However, special consideration should be given to the administration of ETHYOL in patients receiving antihypertensive medications or other drugs that could potentiate hypotension.

Carcinogenesis, Mutagenesis and Impairment of Fertility

No long term animal studies have been performed to evaluate the carcinogenic potential of ETHYOL. ETHYOL was negative in the Ames test and in the mouse micronucleus test. The free thiol metabolite, however, was positive in the Ames test with S9 microsomal fraction in the TA1535 *Salmonella typhimurium* strain and at the TK locus in the mouse L5178Y cell assay. The metabolite was negative in the mouse micronucleus test and negative for clastogenicity in human lymphocytes.

Pregnancy

Pregnancy Category C. ETHYOL (amifostine) has been shown to be embryotoxic in rabbits at doses of 50 mg/kg, approximately sixty percent of the recommended dose in humans on a body surface area basis. There are no adequate and well-controlled studies in pregnant women. ETHYOL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

No information is available on the excretion of ETHYOL or its metabolites into human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, it is recommended that breast feeding be discontinued if the mother is treated with ETHYOL.

ADVERSE REACTIONS

ETHYOL produced a transient reduction in blood pressure in 62% of patients treated. The mean time of onset was 14 minutes into the 15-minute period of ETHYOL infusion, and the mean duration was 6 minutes. In some cases, the infusion had to be prematurely terminated due to a more pronounced drop in systolic blood pressure. In general, the blood pressure returned to normal within 5–15 minutes. Fewer than 3% of patients discontinued ETHYOL due to blood pressure reductions. Short term, reversible loss of consciousness has been reported rarely. Blood pressure reductions during ETHYOL administration have not been reported to cause long-term CNS, cardiovascular or renal sequelae, but clinical studies performed to date have not evaluated the safety of ETHYOL in elderly patients or patients with pre-existing cardiovascular or cerebrovascular conditions.

Hypotension that requires interruption of the ETHYOL Infusion should be treated with fluid infusion and postural management of the patient (supine or Trendelenburg position). If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic, the infusion may be restarted, so that the full dose of ETHYOL can be administered.

Nausea and/or vomiting occur frequently after amifostine infusion and may be severe. In the ovarian cancer randomized study, the incidence of severe nausea/vomiting on day 1 of cyclophosphamide-cisplatin chemotherapy was 10% in patients who did not receive ETHYOL, and 19% in patients who did receive ETHYOL. Other effects which have been described during or following ETHYOL infusion are flushing/feeling of warmth, chills/feeling of coldness, dizziness, somnolence, hiccups and sneezing. These effects have not generally precluded the completion of chemotherapy.

Decrease in serum calcium concentrations is a known pharmacological effect of ETHYOL. At the recommended doses, clinically significant hypocalcemia has occurred rarely (<1%).

Allergic reactions, ranging from mild skin rashes to rigors, have occurred rarely (<1%). There has been no reported occurrence of anaphylaxis with ETHYOL.

OVERDOSAGE

In clinical trials, the maximum single dose of ETHYOL was 1300 mg/m^2. No information is available on single doses higher than this in adults. In the setting of a clinical trial, children have received single ETHYOL doses of up to 2700 mg/m^2 with no unexpected effects. Multiple infusions (up to three) of 740–910 mg/m^2 doses of ETHYOL have been administered within a 24-hour period under study conditions without unexpected effects. Administration of ETHYOL at 2 and 4 hours after the initial dose has not led to increased or cumulative side effects, such as increased nausea and vomiting or hypotension. The most likely symptom of overdosage is hypotension, which should be managed by infusion of normal saline and other supportive measures, as clinically indicated.

DOSAGE AND ADMINISTRATION

In adults, the recommended starting dose of ETHYOL is 910 mg/m^2 administered once daily as a 15-minute i.v. infusion, starting 30 minutes prior to chemotherapy.

The 15-minute infusion is better tolerated than more extended infusions. Further reductions in infusion times have not been systematically investigated.

The infusion of ETHYOL should be interrupted if the systolic blood pressure decreases significantly from the baseline value as listed in the guideline below:

Guideline for Interrupting ETHYOL Infusion Due to Decrease in Systolic Blood Pressure

	Baseline Systolic Blood Pressure (mm Hg)				
	<100	100–119	120–139	140–179	≥180
Decrease in systolic blood pressure during infusion of ETHYOL (mm Hg)	20	25	30	40	50

If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic, the infusion may be restarted so that the full dose of ETHYOL may be administered. If the full dose of ETHYOL cannot be administered, the dose of ETHYOL for subsequent cycles should be 740 mg/m^2.

Only limited experience is available for the usage of ETHYOL in children or elderly patients (more than 70 years of age).

It is recommended that antiemetic medication, including dexamethasone 20 mg i.v. and a serotonin $5HT_3$ receptor antagonist, be administered prior to and in conjunction with ETHYOL. Additional antiemetics may be required based on the chemotherapy drugs administered.

Reconstitution

ETHYOL (amifostine) for Injection is supplied as a sterile lyophilized powder mixture requiring reconstitution for intravenous infusion. Each single-use vial contains 500 mg of amifostine (anhydrous basis) and 500 mg of mannitol.

Prior to intravenous injection, ETHYOL for Injection is reconstituted with 9.5 mL of sterile Sodium Chloride Injection, USP 0.9%. The reconstituted solution (500 mg amifostine/10 mL) is chemically stable for up to 5 hours at room temperature (approximately 25°C) or up to 24 hours under refrigeration (2°C to 8°C).

ETHYOL prepared in polyvinylchloride (PVC) bags at concentrations ranging from 5 mg/mL to 40 mg/mL is chemically stable for up to 5 hours when stored at room temperature (25°C) or up to 24 hours when stored under refrigeration (2°C to 8°C).

CAUTION: Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if cloudiness or precipitate is observed.

Incompatibilities

The compatibility of amifostine with solutions other than 0.9% Sodium Chloride for Injection, or Sodium Chloride solutions with other additives, has not been examined. The use of other solutions is not recommended.

HOW SUPPLIED

ETHYOL (amifostine) for Injection is supplied as a sterile lyophilized powder in 10 mL single-use vials (NDC 17314-3123-1). Each single-use vial contains 500 mg of amifostine (anhydrous basis) and 500 mg of mannitol. The vials are available packaged as 3 vials per carton as follows:

3 pack—3 vials per carton (NDC 17314-3123-3)

Store the lyophilized dosage form in a refrigerator (2°C to 8°C).

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Manufactured by:
Ben Venue, Inc.
Bedford,
Ohio 44146

Marketed by:
Alza Pharmaceuticals
A division of Alza Corporation
Palo Alto,
California 94303

And:
U.S. Bioscience, Inc.
West Conshohocken,
Pennsylvania 19428
1-800-506-4959

Revision Date 3/96 LB2005 PB

Shown in Product Identification Guide, page 304

TESTODERM®

[Tes-tō-derm]

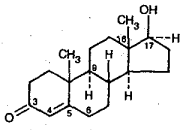
(Testosterone Transdermal System)

CONTROLLED DELIVERY FOR ONCE-DAILY APPLICATION

DESCRIPTION

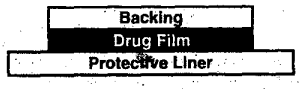
The Testoderm® Testosterone Transdermal System is designed to release controlled amounts of testosterone, the primary circulating endogenous androgen, continuously upon application to scrotal skin.

Two sizes are available to provide nominal in vivo transdermal delivery of 4 or 6 mg testosterone for one day (patients vary in their ability to absorb testosterone transdermally, see Clinical Studies); they have a contact surface area of 40 or 60 cm^2 and contain 10 or 15 mg testosterone USP, respectively. The composition of the two sizes per unit area is identical. Testosterone USP is a white or creamy-white crystalline powder or crystals chemically described as 17-beta hydroxyandrost-4-en-3-one.



$C_{19}H_{28}O_2$m.w.288.43

Testoderm® system is composed of two layers. Proceeding from the outer surface to the film in contact with the skin, these layers are a soft flexible backing of polyethylene terephthalate and a testosterone-containing film of ethylene-vinyl acetate copolymer that contacts the skin surface and modulates the availability of the steroid. A protective liner of fluorocarbon diacrylate or silicone-coated polyester covers the drug film and must be removed before the system can be used.



The active component of the system is testosterone. The remaining components of the system are pharmacologically inactive.

CLINICAL PHARMACOLOGY

Testoderm® releases testosterone, the primary endogenous androgenic hormone. Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature, and fat distribution. DHT is necessary for the normal development of secondary sex characteristics.

Drugs in this class also cause retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.

Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process. Androgens have been reported to stimulate the production of red blood cells by enhancing the production of erythropoietin.

During exogenous administration of androgens, endogenous testosterone release may be inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH).

There is a lack of substantial evidence that androgens are effective in fractures, surgery, or convalescence.

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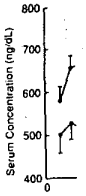

Figure A. *Hou normal young (1983)*

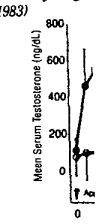

Figure B. *Seru while wearing Systems were a*

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Pharmacokinetics

Endogenous total testosterone serum concentrations in normal males follow a diurnal pattern. Young men and old men have slightly different patterns (Figure A). Daily application of Testoderm® approximates the natural endogenous pattern of serum testosterone of normal males. Following placement of Testoderm® on scrotal skin, the serum testosterone concentration rises to a maximum at 2 to 4 hours and returns toward baseline within approximately 2 hours after system removal. Serum levels reach a plateau at 3 to 4 weeks. Hypogonadal men using Testoderm® therapy have trough serum testosterone concentrations that are about 15% of peak levels. The testosterone levels achieved with Testoderm® therapy generally are within the range for normal men (see also Clinical Studies). The typical pattern achieved with nominal testosterone delivery of 6 mg/day from Testoderm® is shown in Figure B. Scrotal skin is at least five times more permeable to testosterone than other skin sites. Testoderm® will not produce adequate serum testosterone concentration if it is applied to nongenital skin.

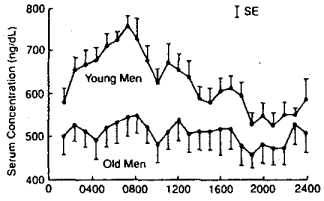

Figure A. *Hourly serum testosterone levels (mean ± SE) in normal young (n=17) and old (n=12) men. (From Bremner, 1983)*

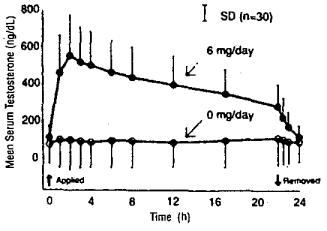

Figure B. *Serum concentration of testosterone (mean ± SD) while wearing a Testoderm® system or placebo (n=30). Systems were applied at 0 hours and removed at 22 hours.*

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes.

Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone easily dissociates from albumin and is presumed to be bioactive. The portion of testosterone bound to SHBG is not considered biologically active. The amount of SHBG in the serum and the total testosterone level will determine the distribution of bioactive and nonbioactive androgen. SHBG-binding capacity is high in prepubertal children, declines during puberty and adulthood and increases again during the later decades of life.

Testosterone is a substrate for conversion to an active metabolite dihydrotestosterone (DHT).

About 90 percent of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6 percent of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver. Testosterone is metabolized to various 17-keto steroids through two different pathways, and the major active metabolites are estradiol and dihydrotestosterone (DHT). Normal concentrations of estradiol in men are 0.8 to 3.5 ng/dL. DHT concentrations in normal male serum are 30 to 85 ng/dL. DHT binds with greater affinity to SHBG than does testosterone. In reproductive tissues, DHT is further metabolized to 3-alpha and 3-beta androstanediol.

In many tissues the activity of testosterone appears to depend on reduction to dihydrotestosterone, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription and cellular changes related to androgen action.

Clinical Studies

After at least 3 weeks of Testoderm® therapy when steady state is obtained, 30 hypogonadal men treated with 6 mg/d systems for 22 hours daily achieved mean maximum serum testosterone concentrations of 593 ng/dL at 2 to 4 hours post-application. Sixty percent of the patients achieved individual maximal testosterone concentrations >500 ng/dL. The mean 24-hour steady-state AUC (area under the curve) value was 9132 ng/dL. The mean DHT serum concentrations ranged from 134 to 162 ng/dL. Normal levels of testosterone have been maintained in patients who have worn the systems for up to six years. DHT levels also remain stable. The increase in serum testosterone concentration is proportional to the size of the system.

The variability of total testosterone concentrations among patients receiving Testoderm® treatment had a coefficient of variation from 35% to 49%. The coefficient of variation of total testosterone concentrations within individual patients was 30% to 41%. This variability is comparable to the values reported in the literature for both normal and hypogonadal men.

In two 12-week clinical studies in 72 hypogonadal men, Testoderm® therapy produced positive effects on mood and sexual behavior. By 5 weeks, 45 patients not previously treated with Testoderm® showed statistically significant increases in sexual activity. Compared to baseline, mean sexual events per week increased for sexual intercourse (0.3 to 0.8), orgasm (0.4 to 1.2), waking erections (1.0 to 3.5), and spontaneous erections (0.4 to 2.8).

Changes in nonfasting serum lipid concentrations were observed during Testoderm® therapy. By three months total cholesterol and high-density lipoprotein cholesterol decreased an average of 8% and 13%, respectively. High-density lipoprotein cholesterol remained stable thereafter. Total cholesterol continued to decrease through two years. At the end of two years, the total cholesterol/high-density lipoprotein cholesterol ratio was not different from pretreatment values.

Composite results of all studies show elevated dihydrotestosterone concentrations and a change in the ratio of testosterone to dihydrotestosterone (T/DHT) during treatment. The range in this ratio was 0.7–12.5, as compared with a ratio of 3.6–15.2 in normal untreated men. The long-term effects of the change in this ratio are not known.

Estradiol levels increased to the normal range with treatment. Sporadic elevations of estradiol above the normal range for men were observed in 3 of 72 patients and these were not associated with feminizing side effects.

INDICATIONS AND USAGE

Testoderm® is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

1. Primary hypogonadism (congenital or acquired)—testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range.
2. Hypogonadotropic hypogonadism (congenital or acquired)—idiopathic gonadotropin or LHRH deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum levels but have gonadotropins in the normal or low range.

Testoderm® therapy has not been evaluated clinically in males under 18 years of age.

CONTRAINDICATIONS

Androgens are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate.

Testoderm® therapy has not been evaluated in women and must not be used in women. Testosterone may cause fetal harm.

Testoderm® systems should not be used in patients with known hypersensitivity to any components of the system.

WARNINGS

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. Testosterone is not known to produce these adverse effects.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility).

Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.

PRECAUTIONS

Information for the Patient

A booklet containing instructions for use of the Testoderm® system is available.

The physician should instruct patients to report any of the following side effects of androgens:

- Too frequent or persistent erections of the penis.
- Any nausea, vomiting, changes in skin color or ankle swelling.

Virilization of female partners has been reported with use of a topical testosterone solution. Percutaneous creams leave as much as 90 mg residual testosterone on the skin. The results from one study indicated that, after removal of a Testoderm® system, the potential for transfer of testosterone to a sexual partner was 6 μg, 1/45th the daily endogenous testosterone production by the female body. Changes in body hair distribution or significant increase in acne of the female partner should be brought to the attention of a physician.

Laboratory Tests

1. Hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia) in patients on long-term androgen therapy.
2. Liver function, prostatic acid phosphatase, prostatic specific antigen, cholesterol, and high-density lipoproteins should be checked periodically.

Drug Interactions

1. Anticoagulants. C-17 substituted derivatives of testosterone, such as methandrostenolone, have been reported to decrease the anticoagulant requirements of patients receiving oral anticoagulants. Patients receiving oral anticoagulant therapy require close monitoring, especially when androgens are started or stopped.
2. Oxyphenbutazone. Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.
3. Insulin. In diabetic patients the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

Drug/Laboratory Test Interactions

Androgens may decrease levels of thyroxin-binding globulin, resulting in decreased total T_4 serum levels and increased resin uptake of T_3 and T_4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal Data. Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Human Data. There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric Use. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.

Pregnancy Category X (See Contraindications).

Teratogenic Effects. Testoderm® therapy must not be used in women.

Nursing Mothers. Testoderm® therapy must not be used in women.

Pediatric Use. Testoderm® therapy has not been evaluated clinically in males under 18 years of age.

ADVERSE REACTIONS

Adverse Reactions with the Testoderm® system

In clinical studies of 104 patients treated with Testoderm® the most common adverse effects reported were local effects. In US clinical trials, most of the 72 patients filling out a daily questionnaire reported scrotal itching, discomfort, or irritation at some time during therapy. Of all the daily questionnaire responses, 7% reported itching, 4% discomfort, and 2% irritation. All topical reactions decreased with duration of use.

The following adverse effects were reported in association with Testoderm® therapy in 104 patients using the product for up to three years; a causal relationship to Testoderm® treatment was not always determined. These effects are listed in decreasing order of occurrence with the number of patients reporting the effect in parentheses: Gynecomastia (5), acne (4), prostatitis/urinary tract infection (4), breast tenderness (3), stroke (2), memory loss (1), pupillary dilation (1), abnormal liver enzymes (1), scrotal cellulitis (1), deep vein phlebitis (1), benign prostatic hyperplasia (1), rectal mucosal lesion over prostate (1), hematuria/bladder cancer (1), papilloma on scrotum (1), and congestive heart failure (1). See CLINICAL PHARMACOLOGY, Clinical Studies subsection, regarding effects on serum lipids.

Adverse Reactions with Injection or Oral Androgen Therapy

Skin and Appendages. Hirsutism, male pattern of baldness, seborrhea, and acne.

Endocrine and Urogenital. Gynecomastia and excessive frequency and duration of penile erections. Oligospermia may occur at high dosages (see CLINICAL PHARMACOLOGY).

Fluid and Electrolyte Disturbances. Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.

Continued on next page

Alza—Cont.

Gastrointestinal. Nausea, cholestatic jaundice, alterations in liver function tests. Rare instances of hepatocellular neoplasms and peliosis hepatitis have occurred (see WARNINGS).
Hematologic. Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, and polycythemia.
Nervous System. Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.
Metabolic. Increased serum cholesterol.
Miscellaneous. Rarely, anaphylactoid reactions.

DRUG ABUSE AND DEPENDENCE

Testoderm® is a Schedule III controlled substance under the Anabolic Steroids Control Act.
With oral administration, it is not possible to achieve clinically significant serum testosterone concentrations in the target organs using the testosterone in Testoderm® due to extensive first-pass metabolism. The half-life of an IM injection of testosterone is about 10 minutes.
Because scrotal skin is at least five times more permeable to testosterone than other skin sites, Testoderm® will not produce adequate serum testosterone concentrations if it is applied to nongenital skin.

OVERDOSAGE

There is one report of acute overdosage with testosterone enanthate: testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident.

DOSAGE AND ADMINISTRATION

Patients should start therapy with a 6 mg/d system applied daily; if scrotal area is inadequate, a 4 mg/d system should be used. Testoderm® should be placed on clean, dry, scrotal skin. Scrotal hair should be dry-shaved for optimal skin contact. Chemical depilatories should not be used (see Patient Information). Testoderm® should be worn 22–24 hours.
After 3–4 weeks of daily system use, blood should be drawn 2–4 hours after system application for determination of serum total testosterone. Because of variability in analytical values among diagnostic laboratories, this laboratory work and later analyses for assessing the effect of the Testoderm® therapy should be performed at the same laboratory.
If patients have not achieved desired results by the end of 6–8 weeks of therapy with Testoderm®, another form of testosterone replacement therapy should be considered.

HOW SUPPLIED

Testoderm® testosterone transdermal system is a Schedule III controlled substance under the Anabolic Steroids Control Act.
Testoderm® systems are supplied as individually pouched systems, 30 per carton.
Testoderm® 4 mg/d (testosterone transdermal system) —each 40 cm^2 system contains 10 mg testosterone USP for nominal delivery of 4 mg for one day.*
Carton of 30 systems ..... NDC 17314-4608-3
Testoderm® 6 mg/d (testosterone transdermal system) —each 60 cm^2 system contains 15 mg testosterone USP for nominal delivery of 6 mg for one day.*
Carton of 30 systems ..... NDC 17314-4609-3
Store at room temperature 15–30°C

REFERENCE

Bremner WJ, Vitiello MV, Prinz PN. *Loss of Circadian Rhythmicity in Blood Testosterone Levels with Aging in Normal Men.* J Clin Endocrin Metab (1983) 56 (6): 1278-1281.
Caution: Federal law prohibits dispensing without prescription.
Manufactured by ALZA Corporation, Palo Alto, California 94304, USA
*See Clinical Studies
Edition: 6/94

PROGESTASERT EDUCATIONAL MATERIAL

All progestasert educational materials are complimentary.
Booklets—Brochures
A. Patient Information Leaflet (English and Spanish)
B. Clinical Evidence Brochure
C. Demonstration Kit
Videos—Audiotapes—Slides
A. Progestasert® System Insertion Technique Videocassette
B. Patient Audiocassette Tape
C. Instructional Slide Program

Information will be superseded by supplements and subsequent editions

American Lecithin Company
115 HURLEY ROAD, UNIT 2B
OXFORD, CT 06478

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PHOSCHOL® OTC

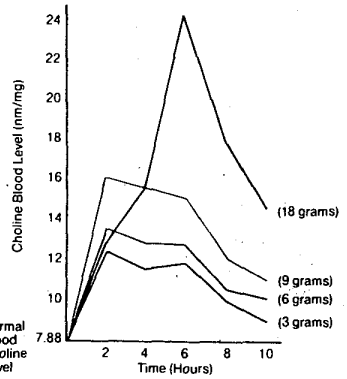
[fos 'kol]
Phosphatidylcholine (highly purified lecithin)
Softgels and Concentrate

DESCRIPTION

PhosChol 900 contains 900 mg of pure phosphatidylcholine in each softgel.
PhosChol Concentrate contains 3000 mg of pure phosphatidylcholine in each teaspoonful.

ACTION & USES

Choline circulating in the blood after PC ingestion is taken up into all cells of the body. The brain has a unique way of ensuring that its nerve cells will receive adequate supplies of circulating choline.
A special protein molecule within the brain's capillaries traps the circulating choline, and then transports it across the blood-brain barrier, into the brain. Once in the brain, choline is incorporated into the brain's own PC, which is an essential and major part of neuronal membranes. Circulating choline transported into the brain has an additional very important function for a special group of nerve cells that make a biochemical, acetylcholine, which is released into synapses as a neurotransmitter. It provides the essential precursor used to synthesize acetylcholine. Moreover, when nerve cells are active, firing frequently and releasing large quantities of acetylcholine, their ability to make adequate amounts of the neurotransmitter requires that they receive adequate amounts of choline from the blood stream. In the absence of adequate choline, the ability of nerve cells to transmit messages to other cells across synapses is impaired and neuronal cell membranes can be depleted of PC causing cell damage. In contrast, when supplemental choline is provided, these messages can be amplified and membrane structure maintained.
PhosChol® brand of highly purified lecithin has been carefully developed to contain the highest concentration of phosphatidylcholine commercially available and can provide for the highest blood choline levels.
Figure 1.
LEVELS OF CHOLINE IN HUMAN PLASMA AFTER THE ADMINISTRATION OF 3, 6, 9, AND 18 GRAM DOSES OF LECITHIN AS PHOSCHOL



(One 9-gram dose at baseline, one 9-gram dose at 4 hours)

ADMINISTRATION

PhosChol® nutritional supplements may be recommended for two purposes:
To guard against low blood choline levels, and to restore blood choline levels in patients suffering from selected brain disorders. Amounts of PC sufficient to increase blood choline levels would help support normal cellular membrane composition and repair; they would also provide sufficient precursor choline for the maintenance of acetylcholine biosynthesis. Taken according to these schedules, dietary supplements of PC are an aid to good health, and protect against low choline stores.
To increase blood choline by 50%, patients should take 3 grams of PhosChol before meals by noon. To double blood choline levels, patients should take 9 grams of PhosChol before meals by noon. If ingestion before meals causes intestinal distress, it is recommended that PhosChol be taken either with meals or immediately thereafter.

ADVERSE REACTIONS

No major side effects have been reported in connection with consumption of large quantities of phosphatidylcholine or commercially available (less pure) lecithin.
Minor side effects may be seen such as increased salivation, nausea and upset stomach.

HOW SUPPLIED

Two strengths as clear, amber colored, one-piece sealed softgels.
PhosChol 900 contains 900 mg of pure phosphatidylcholine in each softgel and is available in bottles of 30, 100 and 300 softgels. Ten softgels a day provide 9 grams of phosphatidylcholine.
PhosChol 565 contains 565 mg of pure phosphatidylcholine and is available in bottles of 100.
One strength as a liquid concentrate.
PhosChol Concentrate contains 3000 mg of pure phosphatidylcholine in each teaspoonful and is available in 8 oz., and 16 oz. bottles. Three teaspoonsful a day provide 9 grams of phosphatidylcholine.

American Red Cross
NATIONAL HEADQUARTERS
BIOMEDICAL SERVICES
431 18th St. N.W.
WASHINGTON, DC 20006-5306

Direct Inquiries to:
Professional Services Department
703-312-8737
FAX: 703-312-8742
Customer Service Department
800-446-8883
FAX: 703-312-8746

ANTIHEMOPHILIC FACTOR (HUMAN) B

Method M
Monoclonal Purified

This product is derived from blood collected from volunteer donors by the American Red Cross Blood Services. The cost of processing, testing and packaging was paid by the American Red Cross Blood Services.

DESCRIPTION

Antihemophilic Factor (Human), Method M, is a sterile, nonpyrogenic, dried preparation of antihemophilic factor (Factor VIII, Factor VIII:C, AHF) in concentrated form with a specific activity range of 2 to 15 AHF International Units/mg of total protein. When reconstituted with the appropriate volume of diluent, it contains approximately 12.5 mg/mL Albumin (Human), 1.5 mg/mL polyethylene glycol (3350), 0.055 M histidine and 0.030 M glycine as stabilizing agents. In the absence of the added Albumin (Human), the specific activity is approximately 2,000 AHF International Units/mg of protein. It also contains, per AHF International Unit, not more than 0.1 ng mouse protein, 18 ng organic solvent [tri(n-butyl)phosphate] and 50 ng detergent (Triton X-100).
See CLINICAL PHARMACOLOGY.
Antihemophilic Factor (Human) is prepared by the Method M process from pooled human plasma by immunoaffinity chromatography utilizing a murine monoclonal antibody to Factor VIII:C, followed by an ion exchange chromatography step for further purification. Method M also includes an organic solvent [tri(n-butyl) phosphate] and detergent (Triton X-100) virus inactivation step designed to reduce the risk of transmission of hepatitis and other viral diseases. However, no procedure has been shown to be totally effective in removing viral infectivity from coagulation factor products.
Each bottle of Antihemophilic Factor (Human) is labeled with the AHF activity expressed in International Units per bottle, which is referenced to the WHO International Standard.
Antihemophilic Factor (Human) is to be administered only intravenously.

HOW SUPPLIED

Antihemophilic Factor (Human), Method M, is available as single dose bottles. Each bottle is labeled with the potency in International Units, and is packaged together with 10 mL of

Process Step No.
1
2
3
4

• Minimun
•• Not dete
••• Not appli

Sterile Water a filter needl NDC 52769-4 Manufacture Baxter Healt Hyland Divis Glendale, CA U.S. License Distributed b + American Blood Servic Washington, October 199

IMMUNE (HUMAN) P SOLVENT/D

This product donors by th of processing can Red Cro

DESCRIPT Immune Glo S/D, is a s preparation rived from l ufactured b process follo tography. T with an org tri(n-butyl) Polygam® cant viral re marized in Polygam® Immunodefi bis virus (SI bies virus (viruses suc (VSV), a m These redu process che cold ethan treatment.[3] [See Table When recon Water for I tains appro at least 90% to 5%, cont ride (appro Stabilizing the followi mL Album glucose, 2 n butyl) phos sorbate 80. solution fo added as de TION secti component given for t The manuf nous (Hum tional che portion is n

Berlex Laboratories—Cont.

half-life of sotalol is prolonged (up to 69 hours) in anuric patients. Sotalol, however, can be partly removed by dialysis with subsequent partial rebound in concentrations when dialysis is completed. Both safety (heart rate, QT interval) and efficacy (arrhythmia control) must be closely monitored.

Transfer to BETAPACE®

Before starting BETAPACE®, previous antiarrhythmic therapy should generally be withdrawn under careful monitoring for a minimum of 2–3 plasma half-lives if the patient's clinical condition permits (see **DRUG INTERACTIONS**). Treatment has been initiated in some patients receiving I.V. lidocaine without ill effect. After discontinuation of amiodarone, BETAPACE® should not be initiated until the QT interval is normalized (see **WARNINGS**).

HOW SUPPLIED

BETAPACE® (sotalol hydrochloride); capsule-shaped light-blue scored tablets imprinted with the strength and "BETAPACE", are available as follows:

NDC 50419–105–10	80 mg strength, bottle of 100
NDC 50419–105–11	80 mg strength, carton of 100 unit dose
NDC 50419–109–10	120 mg strength, bottle of 100
NDC 50419–109–11	120 mg strength, carton of 100 unit dose
NDC 50419–106–10	160 mg strength, bottle of 100
NDC 50419–106–11	160 mg strength, carton of 100 unit dose
NDC 50419–107–10	240 mg strength, bottle of 100
NDC 50419–107–11	240 mg strength, carton of 100 unit dose

Store at controlled room temperature, between 15° to 30°C (59° to 86°F).

Caution: Federal law prohibits dispensing without prescription.

Incidence (%) of Adverse Events and Discontinuations
DAILY DOSE

Body System	160mg (n=832)	240mg (n=263)	320mg (n=835)	480mg (n=459)	640mg (n=324)	Any Dose* (n=1292)	% Patients Discontinued (n=1292)
Body as a whole							
infection	1	2	2	2	3	4	<1
fever	1	2	3	2	2	4	<1
localized pain	1	1	2	2	2	3	<1
Cardiovascular							
dyspnea	5	8	11	15	15	21	2
bradycardia	8	8	9	7	5	16	2
chest pain	4	3	10	10	14	16	<1
palpitation	3	3	8	9	12	14	<1
edema	2	2	5	3	5	8	1
ECG abnormal	4	2	4	2	2	7	1
hypotension	3	4	3	2	3	6	2
proarrhythmia	<1	<1	2	4	5	5	3
syncope	1	1	3	2	5	5	1
heart failure	2	3	2	2	2	5	1
presyncope	1	2	2	4	3	4	<1
peripheral vascular disorder	1	2	1	1	2	3	<1
cardiovascular disorder	1	<1	2	2	2	3	<1
vasodilation	1	<1	1	2	1	3	<1
AICD Discharge	<1	2	2	2	2	3	<1
hypertension	<1	1	1	1	2	2	<1
Nervous							
fatigue	5	8	12	12	13	20	2
dizziness	7	6	11	11	14	20	1
asthenia	4	5	7	8	10	13	1
light-headed	4	3	6	6	9	12	1
headache	3	2	4	4	4	8	<1
sleep problem	1	1	5	5	6	8	<1
perspiration	1	2	3	4	5	6	<1
altered consciousness	2	3	1	2	3	4	<1
depression	1	2	2	2	3	4	<1
paresthesia	1	1	2	3	2	4	<1
anxiety	2	2	2	3	2	4	<1
mood change	<1	<1	1	3	2	3	<1
appetite disorder	1	2	2	1	3	3	<1
stroke	<1	<1	1	1	<1	1	<1
Digestive							
nausea/vomiting	5	4	4	6	6	10	1
diarrhea	2	3	3	3	5	7	<1
dyspepsia	2	3	3	3	3	6	<1
abdominal pain	<1	<1	2	2	2	3	<1
colon problem	2	1	1	<1	2	3	<1
flatulence	1	<1	1	1	2	2	<1
Respiratory							
pulmonary problem	3	3	5	3	4	8	<1
upper respiratory tract problem	1	1	3	4	3	5	<1
asthma	1	<1	1	1	1	2	<1
Urogenital							
genitourinary disorder	1	0	1	1	2	3	<1
sexual dysfunction	<1	1	1	1	3	2	<1
Metabolic							
abnormal lab value	1	2	3	2	1	4	<1
weight change	1	1	1	<1	2	2	<1
Musculoskeletal							
extremity pain	2	2	4	5	3	7	<1
back pain	1	<1	2	2	2	3	<1
Skin and Appendages							
rash	2	3	2	3	4	5	<1
Hematologic							
bleeding	1	<1	1	<1	2	2	<1
Special Senses							
visual problem	1	1	2	4	5	5	<1

*Because patients are counted at each dose level tested, the Any Dose column cannot be determined by adding across the doses.

Information will be superseded by supplements and subsequent editions

Manufactured for:
BERLEX Laboratories, Wayne, NJ 07470
Manufactured by:
A Bristol-Myers Company
Evansville, Indiana 47721
6063801 Rev. 4/96

Shown in Product Identification Guide, page 305

CLIMARA®

℞

[*cli-măr'-a*]
(ESTRADIOL TRANSDERMAL SYSTEM)

PRESCRIBING INFORMATION

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is currently no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

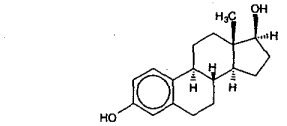
Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

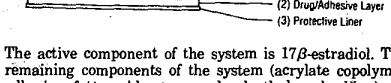
DESCRIPTION

Climara®, estradiol transdermal system, is designed to release 17β-estradiol continuously upon application to intact skin. Two (12.5 and 25.0 sq cm) systems are available to provide nominal *in vivo* delivery of 0.05 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 12.5 or 25.0 sq cm, and contains 3.9 or 7.8 mg of estradiol USP respectively. The composition of the systems per unit area is identical.

Estradiol USP (17β-estradiol) is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.37. The structural formula is:



The Climara® system comprises two layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film, and (2) an acrylate adhesive matrix containing estradiol USP. A protective liner (3) of siliconized or fluoropolymercoated polyester film is attached to the adhesive surface and must be removed before the system can be used.



The active component of the system is 17β-estradiol. The remaining components of the system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

The Climara® system provides systemic estrogen replacement therapy by releasing 17β-estradiol, the major estrogenic hormone secreted by the human ovary.

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. They also contribute to the shaping of the skeleton, maintenace of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone—especially in its sulfate ester form—is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor.

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Estrogens used in therapy are well absorbed through the skin, musous membranes, and gastrointestinal tract. Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms, which are continually interconverted, especially between estrone and estradiol and between esterified and unesterified forms. Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservior for the formation of more active estrogenic species. A certain proportion of the estrogen is excreted into the bile and then reabsorbed from the intestine. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. In contrast, the skin metabolizes estradiol only to a small extent. Therefore, transdermal administration produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates, and requires smaller total doses than does oral therapy. Because estradiol has a short half-life, transdermal administration of estradiol allows a rapid decline in blood levels after the Climara® system is removed.

PHARMACOKINETICS

Transdermal administration of estradiol is reported to produce mean serum concentrations of estradiol comparable to those produced by daily oral administration of estradiol at about 20 times the daily transdermal dose.

In a 3-week multiple-application study in 24 postmenopausal women, the 25.0 sq cm Climara® system produced average peak estradiol concentrations of approximately 100 pg/mL. Trough values at the end of each wear interval were approximately 35 pg/mL. Nearly identical serum curves were seen each week, indicating little or no accumulation of estradiol in the body. Serum estrone peak and trough levels were 60 and 40 pg/mL, respectively. Because estradiol has a short half-life (approximately 1 hour), serum concentrations of estradiol and estrone returned to preapplication levels within 6 to 24 hours after removal of the last system (to less than 17 pg/mL of estradiol and 30 pg/mL estrone.)

Linear pharmacokinetics have been demonstrated for the Climara® system. In a 1-week application study in 54 postmenopausal women, the 25.0 sq cm system produced estradiol serum level profiles and pharmacokinetic parameters that were twice as high as the 12.5 sq cm system. Statistical analyses confirmed the 2:1 dose proportionality.

On average, the Climara® 25.0 sq cm system maintained mean steady-state serum estradiol levels of approximately 70 pg/mL, and the Climara® 12.5 sq cm system maintained mean steady-state serum estradiol levels of approximately 35 pg/mL.

Table 1 summarizes the mean results from four pharmacokinetic studies. All systems were applied on the abdomen for a single 1-week period. C_{max} occurred at approximately 30 hours.

Table 1
Pharmacokinetic Summary

Surface Area (sq cm)	Delivery Rate (mg/day)	C_{max} (pg/mL)	C_{min} (pg/mL)	C_{avg} (pg/mL)
12.5	0.05	58–82	20–32	33–45
25.0	0.1	98–172	39–61	53–93

The relative standard deviation of each pharmacokinetic parameter averaged 50%, which is indicative of the considerable intersubject variability associated with transdermal drug delivery.

Two studies compared a single, 1-week application of the Climara® system with consecutive 3-day and 4-day applications of Estraderm® (a twice-a-week transdermal estradiol system). The Climara® 25.0 sq cm system was compared with the Estraderm® 20 sq cm system (see Figure 1); the Climara® 12.5 sq cm system was compared to the Estraderm® 10 sq cm system (see Figure 2). For a 1-week treatment period, both sizes of Climara® systems maintained significantly lower peak and mean steady-state levels than did the Estraderm® system; however, towards the end of each treatment period, the Climara® systems maintained similar (day 6) or higher (day 7) serum estradiol levels than did the Estraderm® system. As a result, the peak-to-end of application interval trough level fluctuations were 3- to 4-times less with the Climara® system.

Figure 1
Mean Serum Estradiol Levels for a One-Week Application of the Climara® system (25 sq cm) and Consecutive Three-Day and Four-Day Applications of the Estraderm® System (20 sq cm)

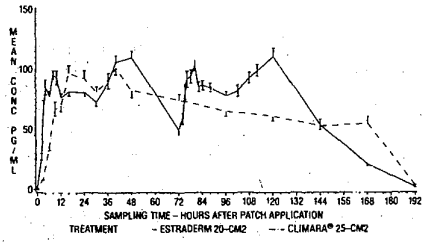
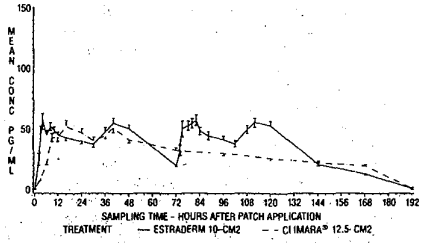


Figure 2
Mean Serum Estradiol Levels for a One-Week Application of the Climara® system (12.5 sq cm) and Consecutive Three-Day and Four-Day Applications of the Estraderm® System (10 sq cm)



INDICATIONS AND USAGE

Climara® is indicated in the:

1. Treatment of moderate to severe vasomotor syptoms associated with the menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.
2. Treatment of vulval and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see Boxed Warning). Estrogens may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders.

WARNINGS

1. **Induction of malignant neoplasms.**

Endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use—with increased risks of 15- to 24-fold for five to ten years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see Precautions).

Breast cancer. While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3–2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

Congenital lesions with malignant potential. Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

2. **Gallbladder disease.** Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens.

3. **Cardiovascular disease.** Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

4. **Elevated blood pressure.** Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use. Ethinyl estradiol and conjugated estrogens have been shown to increase renin substrate. In contrast to these oral estrogens, transdermally administered estradiol has been reported not to affect renin substrate.

5. **Hypercalcemia.** Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped

Continued on next page

Information on the Berlex products appearing here is based on the most current information available at the time of publication closing. Further information for these and other products may be obtained from the Medical Affairs Department, Berlex Laboratories, 300 Fairfield Road, Wayne, New Jersey 07470, 1-800-888-2407. Information on Betaseron and Fludara may be obtained from Berlex Laboratories, 15049 San Pablo Avenue, Richmond, California 94804-0016, 1-800-888-4112.

Berlex Laboratories—Cont.

and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

A. General

1. **Addition of a progestin.** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphological and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens. These include: (1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL) which could diminish the purported cardioprotective effect of estrogen therapy (see Precautions D.4., below); (2) impairment of glucose tolerance; and (3) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point (see Precautions below).

The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

2. ***Cardiovascular risk.*** *A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.*

In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy *without added progestins* and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports: (1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of a higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit. (2) Current medical practice often includes the use of concomitant progestin therapy with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels. (3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS above).

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

3. **Physical examination.** A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.

4. **Hypercoagulability.** Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use.

Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogens users) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.

5. **Familial hyperlipoproteinemia.** Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

6. **Fluid retention.** Because estrogens may cause some degree of fluid retention, conditions which might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

7. **Uterine bleeding and mastodynia.** Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

8. **Impaired liver function.** Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

B. Information for the Patient. See text of Patient Package Insert after the How Supplied section.

C. Laboratory Tests. Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable.

D. Drug/Laboratory Test Interactions.

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and betathromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.
3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.
7. Reduced serum folate concentration.

E. Carcinogenesis, Mutagenesis, and Impairment of Fertility. See CONTRAINDICATIONS and WARNINGS. Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

F. Pregnancy Category X. See CONTRAINDICATIONS and Boxed Warning. Estrogens should not be used during pregnancy.

G. Nursing Mothers. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

ADVERSE REACTIONS

See WARNINGS and Boxed Warning regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia.

The most commonly reported adverse reaction to the Climara® system in clinical trials was skin irritation at the application site. In two well-controlled clinical studies, the overall rate of discontinuation due to skin irritation at the application site was 6.8%; 7.9% for the 12.5 sq cm system and 5.3% for the 25.0 sq cm system compared with 11.5% for the placebo system. In a 3-week comparative skin irritation study with the Estraderm® system, in 95 subjects, no statistically significant differences in irritation were observed. Some degree of irritation at the end of week three was seen in 25% of Estraderm® and 31% of Climara® subjects. Clinically significant irritation (mild erythema associated with symptoms or moderate to severe erythema) was evident at the end of week three in 11% of Estraderm® and 9% of Climara® subjects.

The following additional adverse reactions have been reported with estrogen therapy:

1. **Genitourinary system.**

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting. Increase in size of uterine leiomyomata. Vaginal candidiasis. Change in amount of cervical secretion.

2. **Breasts.**

Tenderness, enlargement.

3. **Gastrointestinal.**

Nausea, vomiting. Abdominal cramps, bloating. Cholestatic jaundice. Increased incidence of gallbladder disease.

4. **Skin.**

Chloasma or melasma that may persist when drug is discontinued. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Loss of scalp hair. Hirsutism.

5. **Eyes.**

Steepening of corneal curvature. Intolerance to contact lenses.

6. **Central nervous system.**

Headache, migraine, dizziness. Mental depression. Chorea.

7. **Miscellaneous.**

Increase or decrease in weight. Reduced carbohydrate tolerance. Aggravation of porphyria. Edema. Changes in libido.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

The adhesive side of the Climara® system should be placed on a clean, dry area of the abdomen. *The Climara® system should not be applied to the breasts.* The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub and remove the system. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the fingers for about 10 seconds, making sure there is good contact, especially around the edges. In the unlikely event that a system should fall off, a new system should be applied for the remainder of the 7-day dosing interval. Only one system should be worn at any one time during the 7-day dosing interval.

Initiation of Therapy

Two (12.5 and 25.0 sq cm) Climara® systems are available. Treatment is usually initiated with the 12.5 sq cm (0.05 mg/day) Climara® system applied to the skin once-weekly. The dose should be adjusted as necessary to control symptoms. Clinical responses (relief of symptoms) at the lowest effective dose should be the guide for establishing administration of the Climara® system, especially in women with an intact uterus. Attempts to taper or discontinue the medication should be made at 3- to 6-month intervals.

In women who are not currently taking oral estrogens, treatment with the Climara® system can be initiated at once. In women who are currently taking oral estrogen, treatment with the Climara® system can be initiated 1 week after withdrawal of oral therapy or sooner if symptoms reappear in less than 1 week.

Therapeutic Regimen

Therapy with the Climara® system is usually administered on a cyclic schedule (e.g., 3 weeks of therapy followed by 1 week without) especially in women with an intact uterus, who are not using concomitant progestin therapy.

HOW SUPPLIED

Climara® (estradiol transdermal system), 0.05 mg/day—each 12.5 sq cm system contains 3.9 mg of estradiol
USP ..... NDC 50419-451-04
Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Climara® (estradiol transdermal system), 0.1 mg/day—each 25.0 sq cm system contains 7.8 mg of estradiol
USP ..... NDC 50419-452-04
Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Do not store above 86°F (30°C). Do not store unpouched. Apply immediately upon removal from the protective pouch.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured for Berlex Laboratories, Wayne, NJ 07470
Manufactured by 3M Pharmaceuticals, St. Paul, MN 55144

INFORMATION FOR THE PATIENT
INTRODUCTION

The Climara® system that your doctor has prescribed for you releases small amounts of estradiol through the skin in a continuous way. Estradiol is the same hormone that your ovaries produce abundantly before menopause. The dose of estradiol you require will depend upon your individual response. The dose is adjusted by the size of the Climara® system used; the systems are available in two sizes.

This leaflet describes when and how to use estrogens, and the risks and benefits of estrogen treatment.

Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks to you of

estrogen use are acceptable because of their benefits. If you use estrogens, check with your doctor to be sure you are using the lowest possible dose that works, and that you don't use them longer than necessary. How long you need to use estrogens will depend on the reason for use.

1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE").
If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

INFORMATION ABOUT CLIMARA®

How The Climara® System Works

The Climara® system contains 17β-estradiol. When applied to the skin as directed below, the Climara® system releases 17β-estradiol, which flows through the skin into the bloodstream.

How and Where to Apply the Climara® System

Each Climara® system is individually sealed in a protective pouch. Tear open this pouch at the indentation (do not use scissors) and remove the system.

A protective liner covers the adhesive side of the system—the side that will be placed against your skin. This liner must be removed before applying the system. Remove the protective liner and discard it. Try to avoid touching the adhesive. Apply the adhesive side of the system to a clean, dry area of the skin on the abdomen. *Do not apply the Climara® system to your breasts.* The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub and remove the system. Apply the system immediately after opening the pouch and removing the protective liner. Press the system firmly in place with the fingers for about 10 seconds, making sure there is a good contact, especially around the edges.

The Climara® system should be worn continuously for one week. You may wish to experiment with different locations when applying a new system, to find ones that are most comfortable for you and where clothing will not rub on the system.

When to Apply the Climara® System

The Climara® system should be changed once weekly. When changing the system, remove the used Climara® system and discard it. Any adhesive that might remain on your skin can be easily rubbed off. Then place the new Climara® system on a different skin site. (The same skin site should not be used again for at least 1 week after removal of the system). Contact with water when you are bathing, swimming, or showering will not affect the system. In the unlikely event that a system should fall off, a new system should be applied for the remainder of the 7-day dosing interval.

USES OF ESTROGEN

(Not every estrogen drug is approved for every use listed in this section. If you want to know which of these possible uses are approved for the medicine prescribed for you, ask your doctor or pharmacist to show you the professional labeling. You can also look up the specific estrogen product in a book called the "Physician's Desk Reference", which is available in many book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.)

- **To reduce moderate or severe menopausal symptoms.**
Estrogens are hormones made by the ovaries of normal women. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the "change of life" or menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes "surgical menopause".
When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women have only mild menopausal symptoms or none at all and do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.
- **To treat vulval and vaginal atrophy** (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.
- **To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.**
- **To treat certain types of abnormal vaginal bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.**
- **To treat certain cancers in special situations, in men and women.**
- **To prevent thinning of bones.**
Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows down bone thinning and may prevent bones from breaking. Lifelong adequate calcium intake, either in the diet (such as dairy products) or by calcium supplements (to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise (like walking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you.
Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister, or aunt. Women who have relatively early menopause, often because their ovaries were removed during an operation ("surgical menopause"), are more likely to develop osteoporosis than women whose menopause happens at the average age.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

- **During pregnancy (see Boxed Warning).**
If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.
- **If you have unusual vaginal bleeding which has not been evaluated by your doctor (see Boxed Warning).**
Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.
- **If you have had cancer.**
Since estrogens increase the risk of certain types of cancer, you should not use estrogens if you have ever had cancer of the breast or uterus, unless your doctor recommends that the drug may help in the cancer treatment. (For certain patients with breast or prostate cancer, estrogens may help).
- **If you have any circulation problems.**
Estrogen drugs should not be used except in unusually special situations in which your doctor judges that you need estrogen therapy so much that the risks are acceptable. Men and women with abnormal blood clotting conditions should avoid estrogen use (see Dangers of Estrogens, below).
- **When they do not work.**
During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.
- **After childbirth or when breastfeeding a baby.**
Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see Dangers of Estrogens, below).
If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health care provider.

DANGERS OF ESTROGENS

- **Cancer of the uterus.**
Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger doses you use. One study showed that after women stop taking estrogens, this higher cancer risk quickly returns to the usual level of risk (as if you had never used estrogen therapy). Three other studies showed that the cancer risk stayed high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk. **IT IS IMPORTANT TO TAKE THE LOWEST DOSE THAT WORKS AND TO TAKE IT ONLY AS LONG AS YOU NEED IT.**
Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see Other Information, below.)
If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.
- **Cancer of the breast.**
Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods. Regular breast examinations by a health professional and monthly self-examination are recommended for all women.
- **Gallbladder disease.**
Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.
- **Abnormal blood clotting.**
Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long-term disability. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:
—Nausea and vomiting.
—Breast tenderness or enlargement.
—Enlargement of benign tumors ("fibroids") of the uterus.
—Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
—A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:

- **See your doctor regularly.**
While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.
- **Reassess your need for estrogens.**
You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

Continued on next page

Information on the Berlex products appearing here is based on the most current information available at the time of publication closing. Further information for these and other products may be obtained from the Medical Affairs Department, Berlex Laboratories, 300 Fairfield Road, Wayne, New Jersey 07470, 1-800-888-2407. Information on Betaseron and Fludara may be obtained from Berlex Laboratories, 15049 San Pablo Avenue, Richmond, California 94804-0016, 1-800-888-4112.

Berlex Laboratories—Cont.

- **Be alert for signs of trouble.**

If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:
Abnormal bleeding from the vagina (possible uterine cancer)
Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)
Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)
Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)
Yellowing of the skin or eyes (possible liver problem)
Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION

1. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctors may prescribe a progestin for you to take together with your estrogen.

You should know, however, that taking estrogens with progestins may have additional risks. These include:

—unhealthy effects on blood fats (especially a lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease);
—unhealthy effects on blood sugar (which might make a diabetic condition worse); and
—a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Some research has shown that estrogens taken *without* progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

2. Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
3. If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about how much to take.
4. Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.
5. This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians' Desk Reference," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

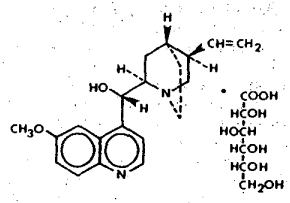
Do not store above 86°F (30°C). Do not store unpouched. Apply immediately upon removal from the protective pouch.
CAUTION: Federal law prohibits dispensing without prescription.
Manufactured for Berlex Laboratories, Wayne, NJ 07470
Manufactured by 3M Pharmaceuticals, St. Paul, MN 55144

617201 January 1995
617300 January 1995
BERLEX LABORATORIES,
WAYNE, NJ 07470
Shown in Product Identification Guide, page 305

QUINAGLUTE ℞
DURA-TABS® TABLETS
[*kwīn'uh glōōt*]
(BRAND OF QUINIDINE GLUCONATE EXTENDED-RELEASE TABLETS, USP)

DESCRIPTION

Quinidine is an antimalarial schizonticide and an antiarrhythmic agent with Class Ia activity; it is the d-isomer of quinine, and its molecular weight is 324.43. Quinidine gluconate is the gluconate salt of quinidine; its chemical name is cinchonan-9-ol, 6'-methoxy-, (9S)-, mono-D-gluconate; its structural formula is:



Its empirical formula is $C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$; and its molecular weight is 520.58, of which 62.3% is quinidine base.
Each QUINAGLUTE DURA-TABS® tablet contains 324 mg of quinidine gluconate (202 mg of quinidine base) in a matrix to provide extended-release; the inactive ingredients include confectioner's sugar, magnesium stearate, corn starch and other ingredients. Meets USP Drug Release Test 4.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism:

The absolute **bioavailability** of quinidine from QUINAGLUTE® is 70–80%. Relative to a solution of quinidine sulfate, the bioavailability of quinidine from QUINAGLUTE® is reported to be 1.03. The less-than-complete bioavailability is thought to be due to first-pass elimination by the liver. Peak serum levels generally appear 3–5 hours after dosing; when the drug is taken with food, absorption is increased in both rate (27%) and extent (17%). The rate and extent of absorption of quinidine from QUINAGLUTE® are not significantly affected by the coadministration of an aluminum-hydroxide antacid.

The **volume of distribution** of quinidine is 2–3 L/kg in healthy young adults, but this may be reduced to as little as 0.5 L/kg in patients with congestive heart failure, or increased to 3–5 L/kg in patients with cirrhosis of the liver. At concentrations of 2–5 mg/L (6.5–16.2 μmol/L), the fraction of quinidine bound to plasma proteins (mainly to α_1-acid glycoprotein and to albumin) is 80–88% in adults and older children, but it is lower in pregnant women, and in infants and neonates it may be as low as 50–70%. Because α_1-acid glycoprotein levels are increased in response to stress, serum levels of total quinidine may be greatly increased in settings such as acute myocardial infarction, even though the serum content of unbound (active) drug may remain normal. Protein binding is also increased in chronic renal failure, but binding abruptly descends toward or below normal when heparin is administered for hemodialysis.

Quinidine **clearance** typically proceeds at 3–5 ml/min/kg in adults, but clearance in children may be twice or three times as rapid. The elimination half-life is 6–8 hours in adults and 3–4 hours in children. Quinidine clearance is unaffected by hepatic cirrhosis, so the increased volume of distribution seen in cirrhosis leads to a proportionate increase in the elimination half-life.

Most quinidine is eliminated hepatically via the action of cytochrome P450IIIA4; there are several different hydroxylated metabolites, and some of these have antiarrhythmic activity.

The most important of quinidine's metabolites is 3-hydroxyquinidine (3HQ), serum levels of which can approach those of quinidine in patients receiving conventional doses of QUINAGLUTE®. The volume of distribution of 3HQ appears to be larger than that of quinidine, and the elimination half-life of 3HQ is about 12 hours.

As measured by antiarrhythmic effects on animals, by QT_c prolongation in human volunteers, or by various *in vitro* techniques, 3HQ has at least half the antiarrhythmic activity of the parent compound, so it may be responsible for a substantial fraction of the effect of QUINAGLUTE® in chronic use.

When the urine pH is less than 7, about 20% of administered quinidine appears unchanged in the urine, but this fraction drops to as little as 5% when the urine is more alkaline. Renal clearance involves both glomerular filtration and active tubular secretion, moderated by (pH-dependent) tubular reabsorption. The net renal clearance is about 1 ml/min/kg in healthy adults.

When renal function is taken into account, quinidine clearance is apparently independent of patient age.

Assays of serum quinidine levels are widely available, but the results of modern assays may not be consistent with results cited in the older medical literature. The serum levels of quinidine cited in this package insert are those derived from specific assays, using either benzene extraction or (preferably) reverse-phase high-pressure liquid chromatography. In matched samples, older assays might unpredictably have given results that were as much as two or three times higher. A typical "therapeutic" concentration range is 2–6 mg/L (6.2–18.5 μmol/L).

Mechanisms of action

In patients with malaria, quinidine acts primarily as an intraerythrocytic schizonticide, with little effect upon sporozites or upon pre-erythrocytic parasites. Quinidine is gametocidal to *Plasmodium vivax* and *P. malariae*, but not to *P. falciparum*.

In cardiac muscle and in Purkinje fibers, quinidine depresses the rapid inward depolarizing sodium current, thereby slowing phase-0 depolarization and reducing the amplitude of the action potential without affecting the resting potential. In normal Purkinje fibers, it reduces the slope of phase-4 depolarization, shifting the threshold voltage upward toward zero. The result is slowed conduction and reduced automaticity in all parts of the heart, with increase of the effective refractory period relative to the duration of the action potential in the atria, ventricles, and Purkinje tissues. Quinidine also raises the fibrillation thresholds of the atria and ventricles, and it raises the ventricular defibrillation threshold as well. Quinidine's actions fall into Class Ia in the Vaughn-Williams classification.

By slowing conduction and prolonging the effective refractory period, quinidine can interrupt or prevent reentrant arrhythmias and arrhythmias due to increased automaticity, including atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia.

In patients with sick sinus syndrome, quinidine can cause marked sinus node depression and bradycardia. In most patients, however, use of quinidine is associated with an increase in the sinus rate.

Like other antiarrhythmic drugs with Class Ia activity, quinidine prolongs the QT interval in a dose-related fashion. This may lead to increased ventricular automaticity and polymorphic ventricular tachycardias, including *torsades de pointes* (see **Warnings**).

In addition, quinidine has anticholinergic activity, it has negative inotropic activity, and it acts peripherally as an α-adrenergic antagonist (that is, as a vasodilator).

CLINICAL EFFECTS

Maintenance of sinus rhythm after conversion from atrial fibrillation: In six clinical trials (published between 1970 and 1984) with a total of 808 patients, quinidine (418 patients) was compared to nontreatment (258 patients) or placebo (132 patients) for the maintenance of sinus rhythm after cardioversion from chronic atrial fibrillation. Quinidine was consistently more efficacious in maintaining sinus rhythm, but a meta-analysis found that mortality in the quinidine-exposed patients (2.9%) was significantly greater than mortality in the patients who had not been treated with active drug (0.8%). Suppression of atrial fibrillation with quinidine has theoretical patient benefits (e.g., improved exercise tolerance; reduction in hospitalization for cardioversion; lack of arrhythmia-related palpitations, dyspnea and chest pain; reduced incidence of systemic embolism and/or stroke), but these benefits have never been demonstrated in clinical trials. Some of these benefits (e.g., reduction in stroke incidence) may be achievable by other means (anticoagulation).

By slowing the atrial rate in atrial flutter/fibrillation, quinidine can decrease the degree of atrioventricular block and can cause an increase, sometimes marked, in the rate at which supraventricular impulses are successfully conducted by the atrioventricular node, with the resultant paradoxical increase in ventricular rate (see **Warnings**).

Non-life-threatening ventricular arrhythmias: In studies of patients with a variety of ventricular arrhythmias (mainly frequent ventricular premature beats and non-sustained ventricular tachycardia, quinidine (total n=502) has been compared with flecainide (n=141), mexiletine (n=246), propafenone (n=53), and tocainide (n=67). In each of these studies, the mortality in the quinidine group was numerically greater than the mortality in the comparator group. When the studies were combined in a meta-analysis quinidine was associated with a statistically significant threefold relative risk of death.

At therapeutic doses, quinidine's only consistent effect upon the surface electrocardiogram is an increase in the QT interval. This prolongation can be monitored as a guide to safety, and it may provide better quidance than serum drug levels (see **Warnings**).

INDICATIONS AND USAGE

Conversion of atrial fibrillation/flutter: In patients with symptomatic atrial fibrillation/flutter whose symptoms are not adequately controlled by measures that reduce the rate of ventricular response, QUINAGLUTE® is indicated as a means of restoring normal sinus rhythm. If this use of QUINAGLUTE® does not restore sinus rhythm within a reasonable time (see **Dosage and Administration**), then QUINAGLUTE® should be discontinued.

Reduction of frequency of relapse into atrial fibrillation/flutter: Chronic therapy with QUINAGLUTE® is indicated for some patients at high risk of symptomatic atrial fibrillation/flutter, generally patients who have had previous episodes of atrial fibrillation/flutter that were so frequent and poorly tolerated as to outweigh, in the judgment of the physician and the patient, the risks of prophylactic therapy with QUINAGLUTE®. The increased risk of death should specifically be considered. QUINAGLUTE® should be used only after alternative measures (e.g., use of other drugs to control the ventricular rate) have been found to be inadequate.

Bock Pharmacal—Cont.

POLY-HISTINE DM® SYRUP ℞

Each 5 ml black-raspberry flavored alcohol-free, sugar free purple syrup contains:

Dextromethorphan HBr	10.0 mg
Phenylpropanolamine HCl	12.5 mg
Brompheniramine Maleate	2.0 mg

HOW SUPPLIED
Bottles of 16 oz.

PRENATE 90® ℞

Each white dye free oval oil- and water-soluble multivitamin/multimineral tablet embossed bock on one side and PN bisect 90 on the other side contains:

Elemental Iron	90.0 mg*
(as Ferrous Fumarate–270 mg)	
Iodine (Potassium Iodide)	150.0 mcg
Calcium (Calcium Carbonate)	250.0 mg
Copper (Cupric Oxide)	2.0 mg
Zinc (Zinc Oxide)	25.0 mg
Folic Acid	1.0 mg
Vitamin A (Acetate)	4000.0 I.U.
Vitamin D (Cholecalciferol)	400.0 I.U.
Vitamin E (Acetate)	30.0 I.U.
(as dl-alpha tocopheryl acetate)	
Vitamin C (Ascorbic Acid)	120.0 mg
Vitamin B_1 (Thiamine Mononitrate)	3.0 mg
Vitamin B_2 (Riboflavin)	3.4 mg
Vitamin B_6 (Pyridoxine HCl)	20.0 mg
Vitamin B_{12} (Cyanocobalamin)	12.0 mcg
Niacinamide	20.0 mg
Docusate Sodium	50.0 mg

*MicroIron™ (A special base to provide delayed therapeutic action)

HOW SUPPLIED
Bottles of 100.
Shown in Product Identification Guide, page 306

ZEPHREX® TABLETS ℞

DESCRIPTION
ZEPHREX® is a white film coated, oval-shaped tablet with a bisect on one side and bock with 460 below the name on the other side.
Each tablet contains:

Pseudoephedrine HCl	60 mg
Guaifenesin	400 mg

HOW SUPPLIED
100's NDC 0563-2624-01
Shown in Product Identification Guide, page 306

ZEPHREX LA® TABLETS ℞

Each timed release* orange, oval-shaped tablet embossed with bock on one side and a Z bisect LA on the other side contains:

Pseudoephedrine HCl	120.0 mg
Guaifenesin	600.0 mg

*In a special base to provide prolonged therapeutic action.

HOW SUPPLIED
Bottles of 100.
Shown in Product Identification Guide, page 306

Check the **PINK** section
to find a particular **BRAND**.

Boehringer Ingelheim Pharmaceuticals, Inc.

A subsidiary of Boehringer Ingelheim Corporation
900 RIDGEBURY ROAD
POST OFFICE BOX 368
RIDGEFIELD, CT 06877-0368

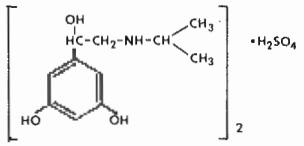
For Medical Information Contact:
(203) 791-6194

ALUPENT® ℞

[al 'u-pent]
(metaproterenol sulfate, USP)
Bronchodilator

Tablets 10 mg		**BI-CODE 74**
Tablets 20 mg		**BI-CODE 72**
Inhalation Aerosol 10 ml		**BI-CODE 70**
Syrup 10 mg/5 ml		**BI-CODE 73**
Inhalation Solution 5%		**BI-CODE 71**
Inhalation Solution	**0.6%**	**BI-CODE 69**
Unit-dose Vials	**0.4%**	**BI-CODE 78**

DESCRIPTION
Alupent® (metaproterenol sulfate USP) Inhalation Aerosol is a bronchodilator administered by oral inhalation. The Alupent Inhalation Aerosol containing 150 mg of metaproterenol sulfate as micronized powder is sufficient medication for 200 inhalations. Each metered dose delivers through the mouthpiece 0.65 mg of metaproterenol sulfate (each ml contains 15 mg). The inert ingredients are dichlorodifluoromethane, dichlorotetrafluoroethane and trichloromonofluoromethane as propellants, and sorbitan trioleate.
Alupent Inhalation Solution is administered by oral inhalation with the aid of a nebulizer or an intermittent positive pressure breathing apparatus (IPPB). It contains Alupent 5% in a pH-adjusted aqueous solution containing benzalkonium chloride and edetate disodium as preservatives.
Alupent Inhalation Solution Unit-dose Vial is administered by oral inhalation with the aid of an IPPB. It contains Alupent 0.4% or 0.6% in a sterile pH-adjusted aqueous solution with edetate disodium and sodium chloride.
Alupent Syrup is administered orally. Each teaspoonful (5 ml) of syrup contains metaproterenol sulfate 10 mg. The inactive ingredients are edetate disodium, FD&C Red No. 40, hydroxyethylcellulose, imitation black cherry flavor, methylparaben, propylparaben, saccharin, sorbitol solution.
Alupent Tablets are administered orally. Each tablet contains metaproterenol sulfate 10 mg or 20 mg. The inactive ingredients are colloidal silicon dioxide, cornstarch, dibasic calcium phosphate, lactose, magnesium stearate.
Chemically, Alupent is 1-(3,5 dihydroxyphenyl)-2-isopropylaminoethanol sulfate, a white crystalline, racemic mixture of two optically active isomers. It differs from isoproterenol hydrochloride by having two hydroxyl groups attached at the meta positions on the benzene ring rather than one at the meta and one at the para position.



metaproterenol sulfate (Alupent)
$(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4$
Mol. Wt. 520.59

CLINICAL PHARMACOLOGY
Alupent® (metaproterenol sulfate USP) is a potent beta-adrenergic stimulator. Alupent Inhalation Aerosol and Inhalation Solution have a rapid onset of action. It is postulated that beta-adrenergic stimulants produce many of their pharmacological effects by activation of adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate to cyclic adenosine monophosphate.
In vitro studies and *in vivo* pharmacologic studies have demonstrated that Alupent® (metaproterenol sulfate USP) has a preferential effect on beta-2 adrenergic receptors compared with isoproterenol. While it is recognized that beta-2 adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that there is a population of beta-2 receptors in the human heart existing in a concentration between 10–50%. The precise functions of these, however, is not yet established (see WARNINGS section).
The pharmacologic effects of beta adrenergic agonist drugs, including Alupent, are at least in part attributable to stimulation through beta adrenergic receptors of intracellular adenyl cyclase, the enzyme which catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (c-AMP). Increased c-AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.
Pharmacokinetics: Absorption, biotransformation and excretion studies in humans following administration by inhalation have shown that approximately 3 percent of the actuated dose is absorbed intact through the lungs.
Absorption, biotransformation and excretion studies in humans following oral administration indicate that an average of less than 10% of the drug is absorbed intact; it is not metabolized by catechol-O-methyl-transferase nor converted to glucuronide conjugates but is excreted primarily as the sulfate conjugate formed in the gut. Pulmonary function tests performed after the administration of Alupent usually show improvement, e.g. an increase in one-second forced expiratory volume (FEV_1), maximum expiratory flow rate, peak expiratory flow rate, forced vital capacity and/or a decrease in airway resistance. The resultant decrease in airway obstruction may relieve the dyspnea associated with bronchospasm.
When administered orally or by inhalation, Alupent decreases reversible bronchospasm. Pulmonary function tests performed concomitantly usually show improvement following aerosol Alupent administration, e.g., an increase in the one-second forced expiratory volume (FEV_1), an increase in maximum expiratory flow rate, an increase in peak expiratory flow rate, an increase in forced vital capacity, and/or a decrease in airway resistance. The resultant decrease in airway obstruction may relieve the dyspnea associated with bronchospasm.
Controlled single- and multiple-dose studies have been performed with pulmonary function monitoring. The duration of effect of a single dose of Alupent Tablets 20 mg or Alupent Syrup (that is, the period of time during which there is a 15% or greater increase in FEV_1) was up to 4 hours.
Controlled single- and multiple-dose studies have been performed with pulmonary function monitoring. The duration of effect of a single dose of two to three inhalations of Alupent Inhalation Aerosol (that is, the period of time during which there is a 20% or greater increase in FEV_1) has varied from 1 to 5 hours.
In repetitive-dosing studies (up to q.i.d.) the duration of effect for a similar dose of Alupent Inhalation Aerosol has ranged from about 1 to 2.5 hours. Present studies are inadequate to explain the divergence in duration of the FEV_1 effect between single- and repetitive-dosing studies, respectively.
Following controlled single dose studies with Alupent Inhalation Solution by an intermittent positive pressure breathing apparatus (IPPB) and by hand-bulb nebulizers, significant improvement (15% or greater increase in FEV_1) occurred within 5 to 30 minutes and persisted for periods varying from 2 to 6 hours.
In these studies, the longer duration of effect occurred in the studies in which the drug was administered by IPPB, i.e., 6 hours, versus 2 to 3 hours when administered by hand-bulb nebulizer. In these studies, the doses used were 0.3 ml by IPPB and 10 inhalations by hand-bulb nebulizer.
In controlled repetitive-dosing studies with Alupent Inhalation Solution by IPPB and by hand-bulb nebulizer the onset of effect occurred within 5 to 30 minutes and duration ranged from 4 to 6 hours. In these studies, the doses used were 0.3 ml b.i.d. or t.i.d. when given by IPPB, and 10 inhalations q.i.d. (no more often than q4h) when given by hand-bulb nebulizer. As in the single dose studies, effectiveness was measured as a sustained increase in FEV_1 of 15% or greater.
In these repetitive-dosing studies there was no apparent difference in duration between the two methods of delivery.
Clinical studies were conducted in which the effectiveness of Alupent Inhalation Solution was evaluated by comparison with that of isoproterenol hydrochloride over periods of two to three months. Both drugs continued to produce significant improvement in pulmonary function throughout this period of treatment.
In two well-controlled studies in children 6 to 12 years of age with acute exacerbation of asthma, 70% of patients receiving Alupent Inhalation Solution (0.1 mL to 0.2 mL) showed improvement in pulmonary function as demonstrated by a 15% increase in FEV_1 above baseline.
Recent studies in laboratory animals (minipigs, rodents and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied tc humans is currently unknown.

INDICATIONS AND USAGE
Alupent® (metaproterenol sulfate USP) is indicated as a bronchodilator for bronchial asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema. Alupent Inhalation Solution 5% is addi-

Boehringer Ingelheim—Cont.

	Programmed Delivery Clonidine *in vivo* Per Day Over 1 Week	Clonidine Content	Size	Code
Catapres-TTS®-1 (clonidine)	0.1 mg	2.5 mg	3.5 cm^2	BI-31
Catapres-TTS®-2 (clonidine)	0.2 mg	5.0 mg	7.0 cm^2	BI-32
Catapres-TTS®-3 (clonidine)	0.3 mg	7.5 mg	10.5 cm^2	BI-33

from 2 months prior to mating. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the oral MRDHD) when the dams were treated on gestation days 6–15. Increases in resorption were observed at much higher dose levels (40 times the oral MRDHD on a mg/kg basis; 4 to 8 times the MRDHD on a mg/m^2 basis) in mice and rats treated on gestation days 1–14 (lowest dose employed in the study was 500 mcg/kg).

No adequate, well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: As clonidine hydrochloride is excreted in human milk, caution should be exercised when CATAPRES (clonidine hydrochloride USP) is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of twelve have not been established (See Warnings on Withdrawal).

ADVERSE REACTIONS

Most adverse effects are mild and tend to diminish with continued therapy. The most frequent (which appear to be dose-related) are dry mouth, occurring in about 40 of 100 patients; drowsiness, about 33 in 100; dizziness, about 16 in 100; constipation and sedation, each about 10 in 100.

The following less frequent adverse experiences have also been reported in patients receiving CATAPRES (clonidine hydrochloride USP), but in many cases patients were receiving concomitant medication and a causal relationship has not been established.

Body as a Whole: Weakness, about 10 in 100 patients; fatigue, about 4 in 100; headache and withdrawal syndrome each about 1 in 100. Also reported were pallor; a weakly positive Coombs' test; increased sensitivity to alcohol; and fever.

Cardiovascular: Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Syncope, Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (i.e. sinus node arrest, functional bradycardia, high degree AV block and arrhythmias) have been reported rarely. Rare cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

Central Nervous System: Nervousness and agitation, about 3 in 100 patients, mental depression, about 1 in 100 and insomnia, about 5 in 1000. Other behavioral changes, vivid dreams or nightmares, restlessness, anxiety, visual and auditory hallucinations and delirium have rarely been reported.

Dermatological: Rash, about 1 in 100 patients; pruritus, about 7 in 1000; hives, angioneurotic edema and urticaria, about 5 in 1000; alopecia, about 2 in 1000.

Gastrointestinal: Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, each about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100; hepatitis, parotitis, constipation, pseudo-obstruction, and abdominal pain, rarely.

Genitourinary: Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000.

Hemotologic: Thrombocytopenia, rarely.

Metabolic Weight gain, about 1 in 100 patients; gynecomastia, about 1 in 1000; transient elevation of blood glucose or serum creatine phosphokinase, rarely.

Musculoskeletal—Muscle or joint pain, about 6 in 1000 and leg cramps, about 3 in 1000.

Oro-otolaryngeal: Dryness of the nasal mucosa was reported.

Ophthalmological: Dryness of the eyes, burning of the eyes and blurred vision were reported.

OVERDOSAGE

Hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis. The frequency of CNS depression may be higher in children than adults. Large overdoses may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma and seizures. Signs and symptoms of overdose generally occur within 30 minutes to two hours after exposure. As little as 0.1 mg of clonidine has produced signs of toxicity in children.

There is no specific antidote for clonidine overdose. Clonidine overdosage may result in the rapid development of CNS depression; therefore, induction of vomiting with ipecac syrup is not recommended. Gastric lavage may be indicated following recent and/or large ingestions. Administration of activated charcoal and/or a cathartic may be beneficial. Supportive care may include atropine sulfate for bradycardia, intravenous fluids and/or vasopressor agents for hypotension and vasodilators for hypertension. Naloxone may be a useful adjunct for the management of clonidine-induced respiratory depression, hypotension and/or coma; blood pressure should be monitored since the administration of naloxone has occasionally resulted in paradoxical hypertension. Tolazoline administration has yielded inconsistent results and is not recommended as first-line therapy. Dialysis is not likely to significantly enhance the elimination of clonidine.

The largest overdose reported to date involved a 28-year old male who ingested 100 mg of clonidine hydrochloride powder. This patient developed hypertension followed by hypotension, bradycardia, apnea, hallucinations, semicoma, and premature ventricular contractions. The patient fully recovered after intensive treatment. Plasma clonidine levels were 60 ng/ml after 1 hour, 190 ng/ml after 1.5 hours, 370 ng/ml after 2 hours, and 120 ng/ml after 5.5 and 6.5 hours. In mice and rats, the oral LD50 of clonidine is 206 and 465 mg/kg, respectively.

DOSAGE AND ADMINISTRATION

Adults: The dose of Catapres® (clonidine hydrochloride USP) must be adjusted according to the patient's individual blood pressure response. The following is a general guide to its administration.

Initial Dose: 0.1 mg tablet twice daily (morning and bedtime). Elderly patients may benefit from a lower initial dose.

Maintenance Dose: Further increments of 0.1 mg per day, may be made at weekly intervals if necessary until the desired response is achieved. Taking the larger portion of the oral daily dose at bedtime may minimize transient adjustment effects of dry mouth and drowsiness. The therapeutic doses most commonly employed have ranged from 0.2 mg to 0.6 mg per day given in divided doses. Studies have indicated that 2.4 mg is the maximum effective daily dose, but doses as high as this have rarely been employed.

Renal Impairment: Dosage must be adjusted according to the degree of impairment, and patients should be carefully monitored. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

HOW SUPPLIED

Catapres® (clonidine hydrochloride USP) is supplied in tablets containing 0.1 mg, 0.2 mg or 0.3 mg of clonidine hydrochloride.

[See table above.]

Store below 86°F (30°C).

Dispense in tight, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

Bottle of 1000	Unit Dose 100
NDC0597-0006-10	NDC0597-0006-61
NDC0597-0007-10	NDC0597-0007-61

Shown in Product Identification Guide, page 306

CATAPRES-TTS® ℞
(clonidine)
Transdermal Therapeutic System
Catapres-TTS-1
Catapres-TTS-2
Catapres-TTS-3
(clonidine)

Programmed delivery in vivo of 0.1, 0.2 or 0.3 mg clonidine per day, for one week.
Prescribing Information

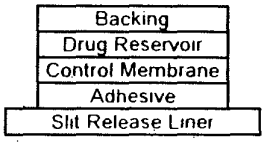
DESCRIPTION

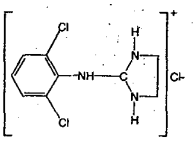
CATAPRES-TTS (clonidine) is a transdermal system providing continuous systemic delivery of clonidine for 7 days at an approximately constant rate. Clonidine is a centrally acting alpha-agonist hypotensive agent. It is an imidazoline derivative with the chemical name 2, 6-dichloro-N-2-imidazolidinylidenebenzenamine and has the following chemical structure:

[See chemical structure at top of next column.]

System Structure and Components: CATAPRES-TTS is a multilayered film, 0.2 mm thick, containing clonidine as the active agent. The system areas are 3.5 cm^2 (CATAPRES-TTS-1), 7.0 cm^2 (CATAPRES-TTS-2) and 10.5 cm^2 (CATAPRES-TTS-3) and the amount of drug released is directly proportional to the area (see Release Rate Concept). The composition per unit area is the same for all three doses. Proceeding from the visible surface towards the surface attached to the skin, there are four consecutive layers 1) a backing layer of pigmented polyester film; 2) a drug reservoir of clonidine, mineral oil, polyisobutylene, and colloiidal silicon dioxide; 3) a microporous polypropylene membrane that controls the rate of delivery of clonidine from the system to the skin surface; 4) an adhesive formulation of clonidine, mineral oil, polyisobutylene, and colloidal silicon dioxide. Prior to use, a protective slit release liner of polyester that covers the adhesive layer is removed.

Corss-section of the sytsem:





$C_9H_9Cl_2N_3 \cdot HCl$ Mol. Wt. 266.56

Release Rate Concept: CATAPRES-TTS is programmed to release clonidine at an approximately constant rate for 7 days. The energy for drug release is derived from the concentration gradient existing between a saturated solution of drug in the system and the much lower concentration prevailing in the skin. Clonidine flows in the direction of the lower concentration at a constant rate, limited by the rate-controlling membrane, so long as a saturated solution is maintained in the drug reservoir.

Following system application to intact skin, clonidine in the adhesive layer staurates the skin site below the system. Clonidine from the drug reservoir then begins to flow through the rate-controlling membrane and the adhesive layer of the system into the systemic circulation via the capillaries beneath the skin. Therapeutic plasma clonidine levels are achieved 2 to 3 days after initial application of CATAPRES-TTS.

The 3.5, 7.0, and 10.5 cm^2 systems deliver 0.1, 0.2, and 0.3 mg of clonidine per day, respectively. To ensure constant release of drug for 7 days, the total drug content of the system is higher than the total amount of drug delivered. Application of a new system to a fresh skin site at weekly intervals continuously maintains therapeutic plasma concentrations of clonidine. If the CATAPRES-TTS is removed and not replaced with a new system, therapeutic plasma clonidine levels will persist for about 8 hours and then decline slowly over several days. Over this time period, blood pressure returns gradually to pretreatment levels.

CLINICAL PHARMACOLOGY

Clonidine stimulates alpha-adrenoreceptors in the brain stem. This action results in reduced sympathetic outflow from the central nervous system and in decreases in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes are intant; therefore, orthostatic symptoms are mild and infrequent.

Acute studies with clonidine hydrochloride in humans have demonstrated a moderate reduction (15–20%) of cardiac output in the supine position with no change in peripheral resistance, at a 45° tilt there is a smaller reduction in cardiac output and a decrease of peripheral resistance.

During long-term therapy, cardiac output tends to return to control values, while peripheral resistance remains decreased. Slowing of the pulse rate has been observed in most patients given clonidine, but the drug does not alter normal hemodynamic responses to exercise.

Tolerance to the antihypertensive effect may develop in some patients, necessitating a reevaluation of therapy.

Other studies in patients have provided evidence of a reduction in plasma renin activity and in the excretion of aldosterone and catecholamines. The exact relationship of these pharmacologic actions to the antihypertensive effect of clonidine has not been fully elucidated.

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Clonidine acutely stimulates the release of growth hormone in children as well as adults but does not produce a chronic elevation of growth hormone with long-term use.

Pharmacokinetics: The plasma half-life of clonidine is 12.7 ± 7 hours. Following oral administration, about 40–60% of the absorbed dose is recovered in the urine as unchanged drug within 24 hours. The remainder of the absorbed dose is metabolized in the liver.

INDICATIONS AND USAGE

CATAPRES-TTs (clonidine) is indicated in the treatment of hypertension. It may be employed alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS

CATAPRES-TTS (clonidine) should not be used in patients with known hypersensitivity to clonidine or to any other component of the therapeutic system.

PRECAUTIONS

General: In patients who have developed localized contact sensitization to CATAPRES-TTS (clonidine) continuation of CATAPRES-TTS or substitution of oral clonidine hydrochloride therapy may be associated with development of a generalized skin rash.

In patients who develop an allergic reaction to CATAPRES-TTS, substitution of oral clonidine hydrochloride may also elicit an allergic reaction (including generalized rash, urticaria, or angioedema).

CATAPRES-TTS should be used with caution in patients with severe coronary insufficiency, conduction distrubances, recent myocardial infarction, cerebrovascular disease, or chronic renal failure.

Withdrawal: Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has, in some cases, resulted in subjective symptoms such as nervousness, agitation, headache, and confusion accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. The likelihood of such reactions to discontinuation of clonidine therapy appears to be greater after administration of higher doses or continuation of concomitant beta-blocker treatment, and special caution is therefore advised in these situations. Rare instances of pulmonary edema, hypertensive encephalopathy, cerebrovascular accident and death have been reported after clonidine withdrawal.

An excessive rise in blood pressure following discontinuation of CATAPRES-TTS therapy can be reversed by administration of oral clonidine HCl or by intravenous phentolamine. If therapy is to be discontinued in patients receiving a beta-blocker and clonidine concurrently, the beta-blocker should be withdrawn several days before cessation of CATAPRES-TTS administration.

In rare instances, loss of blood pressure control has been reported in patients using CATAPRES-TTs® according to the instructions for use.

Perioperative Use: CATAPRES-TTS therapy should not be interrupted during the surgical period. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required. Physicians considering starting CATAPRES-TTS therapy during the perioperative period must be aware that therapetic plasma clonidine levels are not achieved until 2 to 3 days after initial application of CATAPRES-TTs (see DOSAGE AND ADMINISTRATION).

Defibrillation or Cardioversion: The transdermal clonidine systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may increase the risk of arcing, a phenomenon associated with the use of defibrillators.

Information for Patients: Patients should be cautioned against interruption of CATAPRES-TTS therapy without their physicians' advice.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a possible sedative effect of clonidine. They should also be informed that this sedative effect may be increased by concomitant use of alcohol, barbiturates, or other sedating drugs.

Patients should be instructed to consult their physicians promptly about the possible need to remove the patch if they observe moderate to severe localized erythema and/or vesicle formation at the site of application or generalized skin rash.

If a patient experiences isolated, mild localized skin irritation before completing 7 days of use, the system may be removed and replaced with a new system applied to a fresh skin site.

If the system should begin to loosen from the skin after application, the patient should be instructed to place the adhesive overlay directly over the system to ensure adhesion during its 7-day use.

Used CATAPRES-TTS patches contain a substantial amount of their initial drug content which may be harmful to infants and children if accidentally applied or ingested. THEREFORE, PATIENTS SHOULD BE CAUTIONED TO KEEP BOTH USED AND UNUSED CATAPRES TTS PATCHES OUT OF REACH OF CHILDREN. After use, CATAPRES-TTS should be folded in half with the adhesive sides together and discarded away from children's reach.

Instructions for use, storage and disposal of the system are provided at the end of this monograph. These instructions also are included in each bos of Catapres-TTS.

Drug Interactions: Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs. If a patient receiving clonidine is also taking tricyclic antidepressants, the hypotensive effect of clonidine may be reduced, necessitating an increase in the clonidine dose.

Due to potential for additive effects such as bradycardia and AV block, caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction e.g., digitalis, calcium channel blockers and beta-blockers.

Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats (See TOXICOLOGY)

Toxicology: In several studies with oral clonidine hydrochloride, a dose-dependent increase in the incidence and severity of spontaneous retinal degeneration was seen in albino rats treated for six months or longer. Tissue distribution studies in dogs and monkeys showed a concentration of clonidine in the choroid.

In view of the retinal degeneration seen in rats, eye examinations were performed during clinical trials in 908 patients before, and periodically after, the start of clonidine therapy. In 353 of these 908 patients, the eye examinations were carried out over periods of 24 months or longer. Except for some dryness of the eyes, no drug-related abnormal ophthalmological findings were recorded and, according to specialized tests such as electroretinography and macular dazzle, retinal function was unchanged.

In combination with amitriptyline, clonidine hydrochloride administration led to the development of corneal lesions in rats within 5 days.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 132-week study in rats with clonidine administered at a fixed concentration in the diet at 32–46 times the oral maximum recommended daily human dose (MRDHD) revealed no evidence of a carcinogenic potental. Mutagenicity tests were negative. Fertility of male and female rats were unaffected by clonidine doses as high as 150 mcg/kg (approximately 3 times the MRDHD). In a separate experiment, fertility of female rats appeared to be affected at dose levels of 500 to 2000 mcg/kg (10 to 40 times the oral MRDHD).

Pregnancy: *TERATOGENIC EFFECTS Pregnancy Category C* Reproduction studies performed in rabbits at doses up to approximately 3 times the oral maximum recommended daily human dose (MRDHD) of CATAPRES® (clonidine) produced no evidence of a teratogenic or embryotoxic potential in rabbits. In rats, however, doses as low as 1/3 the oral MRDHD of clonidine were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the oral MRDHD) when the dams were treated on gestation days 6–15. Increases in resorption were observed at much higher dose levels (40 times the oral MRDHD) in rats and mice treated on gestation days 1–14 (lowest dose employed in the study was 500 mcg/kg)

No adequate, well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: As clonidine is excreted in human milk, caution should be exercised when CATAPRES-TTS is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of twelve have not been established.

ADVERSE REACTIONS

Clinical trial experience with Catapres-TTS Most systemic adverse effects during CATAPRES-TTS therapy have been mild and have tended to diminish with continued therapy. In a 3-month multiclinic trial of CATAPRES-TTS in 101 hypertensive patients, the systemic adverse reactions were, dry mouth (25 patients) and drowsiness (12) fatigue (6), headache (5), lethargy and sedation (3 each), insomnia, dizziness, impotence/sexual dysfunction, dry throat (2 each) and constipation, nausea, change in taste and nervousness (1 each).

In the above mentioned 3-month controlled clinical trial, as well as other uncontrolled clinical trials, the most frequent adverse reactions were **dermatological** and are described below.

In the 3-month trial, 51 of the 101 patients had localized skin reactions such as erythema (26 patients) and/or pruritus, particularly after using an adhesive overlay throughout the 7-day dosage interval. Allergic contact sensitization to Catapres-TTS was observed in 5 patients. Other skin reactions were localized vesiculation (7 patients), hyperpigmentation (5), edema (3), exoriation (3), burning (3), papules (1), throbbing (1), blanching (1), and a generalized macular rash (1).

In additional clinical experience contact dermatitis resulting in treatment discontinuation was observed in 128 of 673 patients (about 19 in 100) after a mean duration of treatment of 37 weeks. The incidence of contact dermatitis was about 34 in 100 among white women, about 18 in 100 in white men, about 14 in 100 in black women, and approximately 8 in 100 in black men. Analysis of skin reaction data showed that the risk of having to discontinue CATAPRES-TTS treatment because of contact dermatitis was greatest between treatment weeks 6 and 26, although sensitivity may develop either earlier or later in treatment.

In a large-scale clinical acceptability and safety study by 451 physicians in a total of 3539 patients, other allergic reactions were recorded for which a causal relationship to CATAPRES-TTS was not established: maculopapular rash (10 cases), urticaria (2 cases), and angioedema of the fact (2 cases), which also affected the tongue in one of the patients.

Marketing Experience with Catapres-TTS: Other adverse effects reported since the drug has been marketed are listed below by body system. In this setting, an incidence or causal relationship cannot always be accurately determined.

Body as a Whole: Fever, malaise, weakness, pallor, and discontinuation syndrome.

Cardiovascular: Congestive heart failure, cerebrovascular accident, electrocardiographic abnormalities (i.e., conduction distrubances and arrhythmias), chest pain, orthostatic symptoms, syncope, increases in blood pressure, sinus bradycardia and atrioventricular block with and without the use of concomitant digitalis, Raynaud's phenomenon, tachycardia, bradycardia, and palpitations.

Central and Peripheral Nervous System/Psychiatric: Delirium, mental depression, visual and auditory hallucinations, localized numbness, vivid dreams or nightmares, restlessness, anxiety, agitation, irritability, other behavioral changes, and drowsiness.

Dermatological: Angioneurotic edema, localized or generalized rash, hives, urticaria, contact dermatitis, pruritus, alopecia, and localized hypo or hyper pigmentation.

Gastrointestinal: Anorexia, and vomiting.

Genitourinary: Difficult micturation, loss of libido, and decreased sexual activity.

Metabolic: Gynecomastia or breast enlargement and weight gain.

Musculoskeletal: Muscle or joint pain, and leg cramps.

Ophthalmological: Blurred vision, burning of the eyes and dryness of the eyes.

Adverse Events Associated with Oral CATAPARES Therapy: In controlled trials of oral Catapres, the most common adverse reactions were dry mouth (about 40%), drowsiness (about 35%) and sedation (about 8%). The following is a list of adverse events that were reported less frequently. **Body as A Whole:** Weakness, about 10 in 100 patients; fatigue, about 4 in 100; headache and discontinuation syndrome, each about 1 in 100. Also reported were pallor; a weakly positive Coombs' test; increased sensitivity to alcohol; and fever. **Cardiovascular:** Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Syncope, raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (i.e., conduction distrubances and arrhythmias) have been reported rarely. Rare cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis. **Central Nervous System:** nervousness and angitation, about 3 in 100 patients; mental depression, about 1 in 100; insomnia, about 5 in 1000. Other behavioral changes, vivid dreams or nightmares, restlessness, anxiety, visual and auditory hallucinations, and delirium have been reported. **Dermatological:** Rash, about 1 in 100 patients, puritus, about 7 in 1000; hives, angioneurotic edema and urticaria, about 5 in 1000; alopecia, about 2 in 1000. **Gastrointestinal:** Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, each about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100; hepatitis, parotitis and abdominal pain, rarely. **Genitourinary:** Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000. **Hematologic:** Thrombocytopenia, rarely. **Metabolic:** Weight gain, about 1 in 100 patients; gynecomastia, about 1 in 1000; transient elevation of blood glucose or serum creatine phosphokinase, rarely. **Musculoskeletal:** muscle or joint pain, about 6 in 1000 and leg cramps, about 3 in 1000. **Oro-otolaryngeal:** dryness of the nasal mucosa was reported. **Ophthalmological:** dryness of the eyes, burning of the eyes and blurred vision was reported.

OVERDOSAGE

The signs and symptoms of clonidine overdosage may include hypotension, bradycardia, lethargy, irritability, weakness, somnolence, diminished or absent reflexes, miosis, vomiting, and hypoventilation. After large overdoses, reversible cardiac conduction defects or arrhythmias, apnea, seizures, and transient hypertension have been reported.

Continued on next page

Boehringer Ingelheim—Cont.

	Programmed Delivery Clonidine *in vivo* Per Day Over 1 Week	Clonidine Content	Size	Code
Catapres-TTS®-1 (clonidine)	0.1 mg	2.5 mg	3.5 cm^2	BI-31
Catapres-TTS®-2 (clonidine)	0.2 mg	5.0 mg	7.0 cm^2	BI-32
Catapres-TTS®-3 (clonidine)	0.3 mg	7.5 mg	10.5 cm^2	BI-33

If symptoms of overdosage occur, remove all CATAPRES-TTS systems. After their removal, the plasma clonidine levels will persist for about 8 hours, then decline slowly over a period of several days.

There is no specific antidote for clonidine. Treatment should be supportive and may include intravenous fluids as indicated, I.V. atropine sulfate for bradycardia, vasopressor agents in addition to I.V. fluids for hypotension, and vasodilators for hypertension. The alpha-blocker tolazoline has yielded inconsistent results in clonidine overdosage and is therefore not recommended as first-line treatment. The opioid antagonist naloxone may be useful as an adjunct in the management of clonidine intoxication, but cases of a paradoxical hypertensive response to this substance have been reported.

Routine hemodialysis is of limited benefit since a maximum of 5% of total body stores clonidine is removed.

Rare cases of CATAPRES-TTS overdosage due to accidental or deliberate mouthing or ingestion of the patch have been reported, many of them involving children.

In a 28-year old man who ingested 100 mg of clonidine hydrochloride powder, plasma clonidine levels were 60 ng/ml after 1 hour, 190 ng/ml after 1.5 hours, 370 ng/ml after 2 hours, and 120 ng/ml after 5.5 and 6.5 hours. This patient developed hypertension followed by hypotension, bradycardia, apnea, hallucinations, semicoma, and premature ventricular contractions. He fully recovered after intensive treatment. In mice and rats, the oral LD_{50} of clonidine is 206 and 465 mg/kg, respectively.

DOSAGE AND ADMINISTRATION

Apply CATAPRES-TTS (clonidine) once every 7 days to a hairless area of intact skin on the upper outer arm or chest. Each new application of CATAPRES-TTS should be on a different skin site from the previous location. If the system loosens during 7-day wearing, the adhesive overlay should be applied directly over the system to ensure good adhesion. There have been rare reports of the need for patch changes prior to 7 days to maintain blood pressure control.

To initiate therapy, CATAPRES-TTS dosage should be titrated according to individual therapeutic requirements, starting with CATAPRES-TTS-1. If after one or two weeks the desired reduction in blood pressure is not achieved, increase the dosage by adding another CATAPRES-TTS-1 or changing to a larger system. An increase in dosage above two CATAPRES-TTS-3 is usually not associated with additional efficacy.

When substituting CATAPRES-TTS for oral clonidine or for other antihypertensive drugs, physicians should be aware that the antihypertensive effect of CATAPRES-TTS may not commence until 2–3 days after initial application. Therefore, gradual reduction of prior drug dosage is advised. Some or all previous antihypertensive treatment may have to be continued, particularly in patients with more severe forms of hypertension.

Renal Impairment: Dosage must be adjusted according to the degree of impairment, and patients should be carefully monitored. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

HOW SUPPLIED

CATAPRES-TTS-1 (clonidine) and CATAPRES-TTS-2 are supplied as a 4 pouched systems and 4 adhesive overlays per carton, 3 cartons per shipper (NDC 0597-0031-12 and 0597-0032-12, respectively). CATAPRES-TTS 3 is supplied as 4 pouched systems and 4 adhesive overlays per carton (NDC 0597-0033-34). See chart below.

[See table above.]

STORAGE AND HANDLING

Store below 86° F (30° C).

CAUTION: Federal law prohibits dispensing without prescription.

Shown in Product Identification Guide, page 306

COMBIPRES® ℞

[*kom 'be-pres*]

Each tablet contains:
clonidine hydrochloride USP,
0.1 mg or 0.2 mg or 0.3 mg
and chlorthalidone USP, 15 mg
Oral Antihypertensive

Tablets 0.1 ..... BI-CODE 08
Tablets 0.2 ..... BI-CODE 09
Tablets 0.3 ..... BI-CODE 10

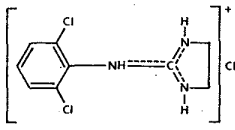
DESCRIPTION

Combipres® is a combination of clonidine hydrochloride (a centrally acting antihypertensive agent) and chlorthalidone (a diuretic). Combipres® is available as tablets for oral administration in three dosage strengths: 0.1/15 mg, 0.2/15 mg and 0.3/15 mg of clonidine hydrochloride/chlorthalidone, respectively.

The inactive ingredients are colloidal silicon dioxide, corn starch, dibasic calcium phosphate, gelatin, glycerin, lactose, magnesium stearate, methylparaben and propylparaben. The Combipres 0.1/15 mg tablet also contains FD&C Red No. 3. The Combipres 0.2/15 mg tablet also contains FD&C Blue No. 1.

Clonidine hydrochloride:

Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. The following is the structural formula:

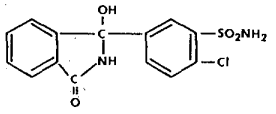


$C_9H_9Cl_2N_3 \cdot HCl$
Mol. Wt. 266.56

Clonidine hydrochloride is an odorless, bitter, white crystalline substance soluble in water and alcohol.

Chlorthalidone

Chlorthalidone is a monosulfamyl diuretic that differs chemically from thiazide diuretics in that a double ring system is incorporated in its structure. It is a racemic mixture of 2-chloro-5-(1- hydroxy-3-oxo-1-isoindolinyl) benzenesulfonamide with the following structural formula:



$C_{14}H_{11}Cl\,N_2O_4S$
Mol. Wt. 338.76

Chlorthalidone is practically insoluble in water, in ether and in chloroform; soluble in methanol; slightly soluble in alcohol.

CLINICAL PHARMACOLOGY

Combipres®:

Combipres produces a more pronounced antihypertensive response than occurs after either clonidine hydrochloride or chlorthalidone alone in equivalent doses.

Clonidine hydrochloride:

Clonidine hydrochloride acts relatively rapidly. The patient's blood pressure declines within 30 to 60 minutes after an oral dose, the maximum decrease occurring within 2 to 4 hours. The plasma level of clonidine hydrochloride peaks in approximately 3 to 5 hours and the plasma half-life ranges from 12 to 16 hours. The half-life increases up to 41 hours in patients with severe impairment of renal function. Following oral administration about 40–60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver.

Clonidine stimulates alpha-adrenoreceptors in the brain stem, resulting in reduced sympathetic outflow from the central nervous system and a decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes are intact and therefore orthostatic symptoms are mild and infrequent. Acute studies with clonidine hydrochloride in humans have demonstrated a moderate reduction (15 to 20%) of cardiac output in the supine position with no change in the peripheral resistance; at a 45° tilt there is a smaller reduction in cardiac output and a decrease of peripheral resistance. During long-term therapy, cardiac output tends to return to control values, while peripheral resistance remains decreased. Slowing of the pulse rate has been observed in most patients given clonidine but the drug does not alter normal hemodynamic response to exercise.

Other studies in patients have provided evidence of a reduction in plasma renin activity and in the excretion of aldosterone and catecholamines, but the exact relationship of these pharmacologic actions to the antihypertensive effect has not been fully elucidated.

Clonidine acutely stimulates growth hormone release in both children and adults, but does not produce a chronic elevation of growth hormone with long-term use.

Tolerance may develop in some patients, necessitating a reevaluation of therapy.

Chlorthalidone:

Chlorthalidone is a long-acting oral diuretic with antihypertensive activity. Its diuretic action commences a mean of 2.6 hours after dosing and continues for up to 72 hours. The drug produces diuresis with increased excretion of sodium and chloride. The diuretic effects of chlorthalidone and the benzothiadiazine (thiazide) diuretics appear to arise from similar mechanisms and the maximal effect of chlorthalidone and the thiazides appears to be similar. The site of action appears to be the distal convoluted tubule of the nephron. The diuretic effects of chlorthalidone lead to decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate, and renal plasma flow. Although the mechanism of action of chlorthalidone and related drugs is not wholly clear, sodium and water depletion appear to provide a basis for its antihypertensive effect. Like the thiazide diuretics, chlorthalidone produces dose-related reductions in serum potassium levels, elevations in serum uric acid and blood glucose, and it can lead to be decreased sodium and chloride levels.

The mean plasma half-life of chlorthalidone is about 40 to 60 hours. It is eliminated primarily as unchanged drug in the urine. Non-renal routes of elimination have yet to be clarified. In the blood, approximately 75% of the drug is bound to plasma proteins.

INDICATIONS AND USAGE

Combipres® (clonidine hydrochloride USP/chlorthalidone USP) is indicated in the treatment of hypertension. **This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.**

CONTRAINDICATIONS

Anuria. Combipres® is contraindicated in patients with known hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

WARNINGS

Chlorthalidone should be used with caution in severe renal disease. In patients with renal disease, chlorthalidone or related drugs may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Chlorthalidone should be used with caution in patients with impaired hepatic function or progressive liver disease, because minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics which are structurally related to chlorthalidone. However, systemic lupus erythematosus has not been reported following chlorthalidone administration.

PRECAUTIONS

Clonidine hydrochloride:

General In patients who have developed localized contact sensitization to Catapres-TTS® (clonidine), substitution of oral clonidine hydrochloride therapy may be associated with the development of a generalized skin rash.

In patients who develop an allergic reaction from Catapres-TTS® (clonidine) that extends beyond the local patch site (such as generalized skin rash, urticaria, or angioedema), oral clonidine hydrochloride substitution may elicit a similar reaction.

As with all antihypertensive therapy, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

Withdrawal Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in subjective symptoms such as nervousness, agitation and headache, accompanied or followed by a rapid rise in blood pressure and ele-

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vated catecholamine concentrations in the plasma, but such occurrences have usually been associated with previous administration of high oral doses (exceeding 1.2 mg/day) and/or with continuation of concomitant beta-blocker therapy. Rare instances of hypertensive encephalopathy and death have been reported. When discontinuing therapy with clonidine hydrochloride, the physician should reduce the dose gradually over 2 to 4 days to avoid withdrawal symptomatology.

An excessive rise in blood pressure following clonidine hydrochloride discontinuance can be reversed by administration of oral clonidine or by intravenous phentolamine. If therapy is to be discontinued in patients receiving beta-blockers and clonidine concurrently, beta-blockers should be discontinued several days before the gradual withdrawal of clonidine hydrochloride.

Perioperative Use Administration of clonidine hydrochloride should be continued to within four hours of surgery and resumed as soon as possible thereafter. The blood pressure should be carefully monitored and appropriate measures instituted to control it as necessary.

Information for Patients Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a potential sedative effect of clonidine. Patients should be cautioned against interruption of clonidine hydrochloride therapy without a physician's advice.

Drug Interactions If a patient receiving clonidine hydrochloride is also taking tricyclic antidepressants, the effect of clonidine may be reduced, thus necessitating an increase in dosage. Clonidine hydrochloride may enhance the CNS-depressive effects of alcohol, barbiturates or other sedatives. Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats (see OCULAR TOXICITY).

OCULAR TOXICITY

In several studies, oral clonidine hydrochloride produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for six months or longer. Tissue distribution studies in dogs and monkeys revealed that clonidine hydrochloride was concentrated in the choroid of the eye. In view of the retinal degeneration observed in rats, eye examinations were performed in 908 patients prior to the start of clonidine hydrochloride therapy, who were then examined periodically thereafter. In 353 of these 908 patients, examinations were performed for periods of 24 months or longer. Except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings were recorded and clonidine hydrochloride did not alter retinal function as shown by specialized tests such as the electroretinogram and macular dazzle.

In rats, clonidine hydrochloride in combination with amitriptyline produced corneal lesions within 5 days.

Carcinogenesis, Mutagenesis, Impairment of Fertility In a 132-week (fixed concentraiton) dietary administration study in rats, clonidine hydrochloride administered at 32 to 46 times the maximum recommended daily human oral dose was unassociated with evidence of carcinogenic potential. Fertility of male or female rats was unaffected by clonidine hydrochloride doses as high as 150 mcg/kg or about 3 times the maximum recommended daily human oral dose (MRDHD). Fertility of female rats did, however, appear to be affected (in another experiment) at dose levels of 500 to 2000 mcg/kg or 10 to 40 times the MRDHD.

Usage in Pregnancy

TERATOGENIC EFFECTS Pregnancy Category C. Reproduction studies performed in rabbits at doses up to approximately 3 times the maximum recommended daily human dose (MRDHD) of clonidine hydrochloride have revealed no evidence of teratogenic or embryotoxic potential. In rats however, doses as low as $\frac{1}{3}$ the MRDHD were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the MRDHD) when dams were treated days 6–15 of gestation. Increased resorptions were observed at much higher levels (40 times the MRDHD) in rats and mice treated days 1–14 of gestation (lowest dose employed in that study was 500 mcg/kg). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers As clonidine hydrochloride is excreted in human milk, caution should be exercised when it is administered to a nursing woman.

Pediatric Use Safety and effectiveness in the pediatric population have not been established.

Chlorthalidone: **General**

Hypokalemia and other electrolyte abnormalities, including hyponatremia and hypochloremic alkalosis, are common in patients receiving chlorthalidone. These abnormalities are dose-related but may occur even at the lowest marketed doses of chlorthalidone. Serum electrolytes should be determined before initiating therapy and at periodic intervals during therapy. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. All patients taking chlorthalidone should be observed for clinical signs of electrolyte imbalance, including dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, palpitations and gastrointestinal disturbances, such as nausea and vomiting. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather: appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In cases of actual salt depletion, appropriate replacement is the therapy of choice.

Uric Acid Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving chlorthalidone.

Other Increases in serum glucose may occur and latent diabetes mellitus may become manifest during chlorthalidone therapy (see PRECAUTIONS Drug Interactions). Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Information for Patients Patients should inform their doctor if they have: 1) had an allergic reaction to chlorthalidone or other diuretics or have asthma 2) kidney disease 3) liver disease 4) gout 5) systemic lupus erythematosus, or 6) been taking other drugs such as cortisone, digitalis, lithium carbonate, or drugs for diabetes.

Patients should be cautioned to contact their physician if they experience any of the following symptoms of potassium loss: excess thirst, tiredness, drowsiness, restlessness, muscle pains or cramps, nausea, vomiting or increased heart rate or pulse.

Patients should also be cautioned that taking alcohol can increase the chance of dizziness occurring.

Laboratory Tests Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids.

Drug Interactions Chlorthalidone may add to or potentiate the action of other antihypertensive drugs. Insulin requirements in diabetic patients may be increased, decreased or unchanged. Higher dosage of oral hypoglycemic agents may be required. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Lithium renal clearance is reduced by chlorthalidone, increasing the risk of lithium toxicity.

Drug/Laboratory Test Interactions Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Carcinogenesis, Mutagenesis, Impairment of Fertility No information is available.

Usage in Pregnancy

TERATOGENIC EFFECTS Pregnancy Category B. Reproduction studies have been performed in the rat and the rabbit at doses up to 420 times the human dose and have revealed no evidence of harm to the fetus due to chlorthalidone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NON-TERATOGENIC EFFECTS Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in the adult.

Nursing Mothers Thiazides are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from chlorthalidone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

Combipres® is generally well tolerated. Most adverse effects are mild and tend to diminish with continued therapy. The most frequent (which appear to be dose-related) are dry mouth, occurring in about 40 to 100 patients; drowsiness, about 33 in 100; dizziness, about 16 in 100; constipation and sedation, each about 10 in 100.

In addition to the reactions listed above, certain less frequent adverse experiences, which are shown below, have also been reported in patients receiving the component drugs of Combipres® but in many cases patients were receiving concomitant medication and a causal relationship has not been established:

Clonidine hydrochloride:

Gastrointestinal Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, each about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100; rare reports of hepatitis; parotitis, rarely.

Metabolic Weight gain, about 1 in 100 patients; gynecomastia, about 1 in 1000, transient elevation of blood glucose or serum creatine phosphokinase, rarely.

Central Nervous System Nervousness and agitation, about 3 in 100 patients; mental depression, about 1 in 100; headache, about 1 in 100; insomnia, about 5 in 1000. Vivid dreams or nightmares, other behavioral changes, restlessness, anxiety, visual and auditory hallucinations and delirium have been reported.

Cardiovascular Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities i.e. conduction disturbances and arrhythmias have been reported rarely. Rare cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

Dermatological Rash, about 1 in 100 patients; pruritus, about 7 in 1000; hives, angioneurotic edema and urticaria, about 5 in 1000, alopecia, about 2 in 1000.

Genitourinary Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000.

Other Weakness, about 10 in 100 patients; fatigue, about 4 in 100; discontinuation syndrome, about 1 in 100; muscle or joint pain, about 6 in 1000 and cramps of the lower limbs, about 3 in 1000. Dryness, burning of the eyes, blurred vision, dryness of the nasal mucosa, pallor, weakly positive Coombs' test, increased sensitivity to alcohol and fever have been reported.

Chlorthalidone:

Gastrointestinal Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis.

Central Nervous System Dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Dermatologic-Hypersensitivity Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis).

Cardiovascular Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics.

Other adverse reactions Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence.

Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

OVERDOSAGE

Clonidine hydrochloride:

The signs and symptoms of clonidine hydrochloride overdosage include hypotension, bradycardia, lethargy, irritability, weakness, somnolence, diminished or absent reflexes, miosis, vomiting and hypoventilation. With large overdoses, reversible cardiac conduction defects or arrhythmias, apnea, seizures and transient hypertension have been reported. The oral LD_{50} of clonidine in rats was 465 mg/kg, and in mice 206 mg/kg.

The general treatment of clonidine hydrochloride overdosage may include intravenous fluids as indicated. Bradycardia can be treated with intravenous atropine sulfate and hypotension with dopamine infusion in addition to intravenous fluids. Hypertension, associated with overdosage, has been treated with intravenous furosemide or diazoxide or alpha-blocking agents such as phentolamine. Tolazoline, an alpha-blocker, in intravenous doses of 10 mg at 30-minute intervals, may reverse clonidine's effects if other efforts fail. Routine hemodialysis is of limited benefit, since a maximum of 5% of circulating clonidine is removed.

In a patient who ingested 100 mg clonidine hydrochloride, plasma clonidine levels were 60 ng/ml (one hour), 190 ng/ml (1.5 hours), 370 ng/ml (two hours) and 120 ng/ml (5.5 and 6.5 hours). This patient developed hypertension followed by hypotension, bradycardia, apnea, hallucinations, semicoma, and premature ventricular contractions. The patient fully recovered after intensive treatment.

Chlorthalidone:

Symptoms of acute overdosage include nausea, weakness, dizziness and disturbances of electrolyte balance. The oral LD_{50} of the drug in the mouse and the rat is more than 25,000 mg/kg body weight. The minimum lethal dose (MLD) in humans has not been established. There is no specific antidote

Continued on next page

Boehringer Ingelheim—Cont.

but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose-saline with potassium, administered with caution.

DOSAGE AND ADMINISTRATION

The dosage must be determined by individual titration. (See INDICATIONS AND USAGE.)

Chlorthalidone is usually initiated at a dose of 25 mg once daily and may be increased to 50 mg if the response is insufficient after a suitable trial.

Clonidine hydrochloride is usually initiated at a dose of 0.1 mg twice daily. Elderly patients may benefit from a lower initial dose. Further increments of 0.1 mg/day may be made if necessary until the desired response is achieved. The therapeutic doses most commonly employed have ranged from 0.2 to 0.6 mg per day in divided doses.

One Combipres® (clonidine hydrochloride/chlorthalidone) Tablet administered once or twice daily can be used to administer a minimum of 0.1 mg clonidine hydrochloride and 15 mg chlorthalidone to a maximum of 0.6 mg clonidine hydrochloride and 30 mg chlorthalidone.

HOW SUPPLIED

Combipres® 0.1/15 mg (each tablet contains clonidine hydrochloride USP, 0.1 mg + chlorthalidone USP, 15 mg) tablets are pink, oval shaped and single scored with the marking BI 8. Available in bottles of 100 (NDC 0597-0008-01) and 1000 (NDC 0597-0008-10).

Combipres® 0.2/15 mg (each tablet contains clonidine hydrochloride USP 0.2 mg +chlorthalidone USP, 15 mg) tablets are blue, oval shaped and single scored with the marking BI 9. Available in bottles of 100 (NDC 0597-0009-01) and 1000 (NDC 0597-0009-10).

Combipres® 0.3/15 mg (each tablet contains clonidine hydrochloride USP, 0.3 mg + chlorthalidone USP, 15 mg) tablets are white, oval shaped and single scored with the marking BI 10. Available in bottles of 100 (NDC 0597-0010-01).

Store below 86°F (30°C). Avoid excessive humidity.

Dispense in tight, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

CM-PI-4/91

Shown in Product Identification Guide, page 306

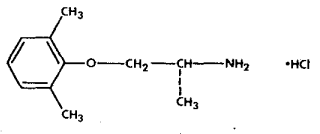
MEXITIL® ℞
(mexiletine hydrochloride)
Oral Antiarrhythmic
Capsules of

150 mg	**BI-CODE 66**
200 mg	**BI-CODE 67**
250 mg	**BI-CODE 68**

DESCRIPTION

Mexitil® (mexiletine hydrochloride) is an orally active antiarrhythmic agent available as 150 mg, 200 mg and 250 mg capsules. 100 mg of mexiletine hydrochloride is equivalent to 83.31 mg of mexiletine base. It is a white to off-white crystalline powder with a slightly bitter taste, freely soluble in water and in alcohol. Mexitil® has a pKa of 9.2.

Chemically, Mexitil® is 1-methyl-2-(2,6-xylyloxy)-ethylamine hydrochloride and has the following structural formula:



mexiletine hydrochloride (USP)
$C_{11}H_{17}NO \cdot HCl$ (MEXITIL) Mol. Wt. 215.73

Mexitil Capsules contain the following inactive ingredients: colloidal silicon dioxide, cornstarch, magnesium stearate, titanium dioxide, gelatin, FD&C Red No. 40, D&C Red No. 28, and FD&C Blue No. 1; the Mexitil 150 mg and 250 mg capsules also contain FD&C Yellow No. 10. Mexitil® capsules may contain one or more of the following components: sodium lauryl sulfate, sodium propionate, edetate calcium disodium, benzyl alcohol, carboxymethylcellulose sodium, glycerin, butylparaben, propylparaben, methylparaben, pharmaceutical glaze, ethylene glycol monoethyl ether, soya lecithin, dimethylpolysiloxane, refined shellac (food grade) and other inactive ingredients.

CLINICAL PHARMACOLOGY

Mechanism of Action Mexitil® (mexiletine hydrochloride USP) is a local anesthetic, antiarrhythmic agent, structurally similar to lidocaine, but orally active. In animal studies, Mexitil has been shown to be effective in the suppression of induced ventricular arrhythmias, including those induced by glycoside toxicity and coronary artery ligation. Mexitil®, like lidocaine, inhibits the inward sodium current, thus reducing the rate of rise of the action potential, Phase 0. Mexitil® decreased the effective refractory period (ERP) in Purkinje fibers. The decrease in ERP was of lesser magnitude than the decrease in action potential duration (APD), with a resulting increase in the ERP/APD ratio.

Electrophysiology in Man Mexiletine is a Class 1B antiarrhythmic compound with electrophysiologic properties in man similar to those of lidocaine, but dissimilar from quinidine, procainamide, and disopyramide.

In patients with normal conduction systems, Mexitil® has a minimal effect on cardiac impulse generation and propagation. In clinical trials, no development of second-degree or third-degree AV block was observed. Mexitil did not prolong ventricular depolarization (QRS duration) or repolarization (QT intervals) as measured by electrocardiography. Theoretically, therefore, Mexitil® may be useful in the treatment of ventricular arrhythmias associated with a prolonged QT interval.

In patients with pre-existing conduction defects, depression of the sinus rate, prolongation of sinus node recovery time, decreased conduction velocity and increased effective refractory period of the intraventricular conduction system have occasionally been observed.

The antiarrhythmic effect of Mexitil® has been established in controlled comparative trials against placebo, quinidine, procainamide and disopyramide. Mexitil®, at doses of 200–400 mg q8h, produced a significant reduction of ventricular premature beats, paired beats, and episodes of non-sustained ventricular tachycardia compared to placebo and was similar in effectiveness to the active agents. Among all patients entered into the studies, about 30% in each treatment group had a 70% or greater reduction in PVC count and about 40% failed to complete the three-month studies because of adverse effects. Follow-up of patients from the controlled trials has demonstrated continued effectiveness of Mexitil in long-term use.

Hemodynamics Hemodynamic studies in a limited number of patients, with normal or abnormal myocardial function, following oral administration of Mexitil, have shown small, usually not statistically significant, decreases in cardiac output and increases in systemic vascular resistance, but no significant negative inotropic effect. Blood pressure and pulse rate remain essentially unchanged. Mild depression of myocardial function, similar to that produced by lidocaine, has occasionally been observed following intravenous Mexitil therapy in patients with cardiac disease.

Pharmacpkinetics Mexitil is well absorbed (~90%) from the gastrointestinal tract. Unlike lidocaine, its first-pass metabolism is low. Peak blood levels are reached in two to three hours. In normal subjects, the plasma elimination half-life of Mexitil is approximately 10–12 hours. It is 50–60% bound to plasma protein, with a volume of distribution of 5–7 liters/kg. Mexitil is metabolized in the liver. Approximately 10% is excreted unchanged by the kidney. While urinary pH does not normally have much influence on elimination, marked changes in urinary pH influence the rate of excretion: acidification accelerates excretion, while alkalinization retards it.

Several metabolites of mexiletine have shown minimal antiarrhythmic activity in animal models. The most active is the minor metabolite N-methylmexiletine, which is less than 20% as potent as mexiletine. The urinary excretion of N-methylmexiletine in man is less than 0.5%. Thus the therapeutic activity of Mexitil is due to the parent compound.

Hepatic impairment prolongs the elimination half-life of Mexitil. In eight patients with moderate to severe liver disease, the mean half-life was approximately 25 hours.

Consistent with the limited renal elimination of Mexitil, little change in the half-life has been detected in patients with reduced renal function. In eight patients with creatinine clearance less than 10 ml/min, the mean plasma elimination half-life was 15.7 hours; in seven patients with creatinine clearance between 11–40 ml/min, the mean half-life was 13.4 hours.

The absorption rate of Mexitil is reduced in clinical situations such as acute myocardial infarction in which gastric emptying time is increased. Narcotics, atropine and magnesium-aluminum hydroxide have also been reported to slow the absorption of Mexitil. Metoclopramide has been reported to accelerate absorption.

Mexiletine plasma levels of at least 0.5 mcg/ml are generally required for therapeutic response. An increase in the frequency of central nervous system adverse effects has been observed when plasma levels exceed 2.0 mcg/ml. Thus the therapeutic range is approximately 0.5 to 2.0 mcg/ml. Plasma levels within the therapeutic range can be attained with either three times daily or twice daily dosing but peak to trough differences are greater with the latter regimen, creating the possibility of adverse effects at peak and arrhythmic escape at trough. Nevertheless, some patients may be transferred successfully to the twice daily regimen (See DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

Mexitil® is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening. Because of the proarrhythmic effects of Mexitil, its use with lesser arrhythmias is generally not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided.

Initiation of Mexitil treatment, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital.

Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmias.

CONTRAINDICATIONS

Mexitil® (mexiletine hydrochloride USP) is contraindicated in the presence of cardiogenic shock or pre-existing second- or third-degree AV block (if no pacemaker is present).

WARNINGS Mortality: In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicentered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to carefully matched placebo-treated groups (3.0%). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) is uncertain. Considering the known proarrhythmic properties of Mexitil and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of Mexitil as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular antiarrhythmia.

Acute Liver Injury In postmarketing experience abnormal liver function tests have been reported, some in the first few weeks of therapy with Mexitil® (mexiletine hydrochloride). Most of these have been observed in the setting of congestive heart failure or ischemia and their relationship to Mexitil® has not been established.

PRECAUTIONS

General If a ventricular pacemaker is operative, patients with second or third degree heart block may be treated with Mexitil® (mexiletine hydrochloride) if continuously monitored. A limited number of patients (45 of 475 in controlled clinical trials) with pre-existing first degree AV block were treated with Mexitil; none of these patients developed second or third degree AV block. Caution should be exercised when it is used in such patients or in patients with pre-existing sinus node dysfunction or intraventricular conduction abnormalities.

Like other antiarrhythmics Mexitil® (mexiletine hydrochloride) can cause worsening of arrhythmias. This has been uncommon in patients with less serious arrhythmias (frequent premature beats or non-sustained ventricular tachycardia: see ADVERSE REACTIONS), but is of greater concern in patients with life-threatening arrhythmias such as sustained ventricular tachycardia. In patients with such arrhythmias subjected to programmed electrical stimulation or to exercise provocation, 10–15% of patients had exacerbation of the arrhythmia, a rate not greater than that of other agents.

Mexitil should be used with caution in patients with hypotension and severe congestive heart failure because of the potential for aggravating these conditions.

Since Mexitil is metabolized in the liver, and hepatic impairment has been reported to prolong the elimination half-life of Mexitil, patients with liver disease should be followed carefully while receiving Mexitil. The same caution should be observed in patients with hepatic dysfunction secondary to congestive heart failure.

Concurrent drug therapy or dietary regimens which may markedly alter urinary pH should be avoided during Mexitil therapy. The minor fluctuations in urinary pH associated with normal diet do not affect the excretion of Mexitil.

SGOT Elevation and Liver Injury In three-month controlled trials, elevations of SGOT greater than three times the upper limit of normal occurred in about 1% of both mexiletine-treated and control patients. Approximately 2% of patients in the mexiletine compassionate use program had elevations of SGOT greater than or equal to three times the upper limit of normal. These elevations frequently occurred in association with identifiable clinical events and therapeutic measures such as congestive heart failure, acute myocardial infarction, blood transfusions and other medications. These

CibaGeneva—Cont.

OVERDOSAGE

Acute Toxicity

No deaths due to acute poisoning with Esimil have been reported.

Oral LD_{50}'s in rats (mg/kg): guanethidine, 1262; hydrochlorothiazide, 2750.

Signs and Symptoms

Guanethidine. Postural hypotension (with dizziness, blurred vision, and possibly syncope when standing), shock, and bradycardia are most likely to occur; diarrhea (possibly severe), nausea, and vomiting may also occur. Unconsciousness is unlikely if adequate blood pressure and cerebral perfusion can be maintained by placing the patient in the supine position and by administering other treatment as required.

Hydrochlorothiazide. The most prominent feature of poisoning is acute loss of fluid and electrolytes.

Cardiovascular: Tachycardia, hypotension, shock.

Neuromuscular: Weakness, confusion, dizziness, cramps of the calf muscles, paresthesia, fatigue, impairment of consciousness.

Digestive: Nausea, vomiting, thirst.

Renal: Polyuria, oliguria, or anuria (due to hemoconcentration).

Laboratory Findings: Hypokalemia, hyponatremia, hypochloremia, alkalosis, increased BUN (especially in patients with renal insufficiency).

Combined Poisoning: Signs and symptoms may be aggravated or modified by concomitant intake of antihypertensive medication, barbiturates, digitalis (hypokalemia), corticosteroids, narcotics, or alcohol.

Treatment

There is no specific antidote.

The stomach contents should be evacuated. An activated charcoal slurry should be instilled and laxatives given, if conditions permit.

If hypotension or shock occurs, the patient's legs should be kept raised, and lost fluid and electrolytes (potassium, sodium) should be replaced. Renal function should be monitored until conditions become normal.

In sinus bradycardia, atropine should be administered.

In previously normotensive patients, treatment has consisted essentially of restoring blood pressure and heart rate to normal by keeping the patient in the supine position. Normal homeostatic control usually returns gradually over a 72-hour period in these patients.

In previously hypertensive patients, particularly those with impaired cardiac reserve or other cardiovascular-renal disease, intensive treatment may be required to support vital functions and to control cardiac irregularities that might be present. The supine position must be maintained; if vasopressors are required, they must be used with extreme caution, since guanethidine may increase responsiveness, causing a rise in blood pressure and development of cardiac arrhythmias.

Diarrhea, if severe or persistent, should be treated with anticholinergic agents to reduce intestinal hypermotility, and hydration and electrolyte balance should be maintained.

Since guanethidine is excreted slowly, cardiovascular and renal function should be monitored for a few days.

DOSAGE AND ADMINISTRATION

Dosage should be determined by titration of individual components (see boxed WARNING). Once the patient has successfully been given titrated doses of the individual components, Esimil may be substituted if the titrated doses are the same as those in the fixed combination.

When combined with other antihypertensive agents, doses of hydrochlorothiazide in excess of 50 mg should be avoided. Therefore, since each Esimil tablet contains 25 mg of hydrochlorothiazide, the daily dosage of this fixed combination should not exceed two tablets. If further blood pressure control is indicated, additional doses of guanethidine or other nondiuretic antihypertensive agents should be considered.

Before using any guanethidine-containing product, at least 1 week should elapse after MAO inhibitors (see CONTRAINDICATIONS) or ganglionic blockers have been discontinued.

HOW SUPPLIED

Tablets—round, white, scored (imprinted CIBA 47)
10 mg of guanethidine monosulfate
25 mg of hydrochlorothiazide
Bottles of 100 ..... NDC 0083-0047-30

Do not store above 86°F (30°C).

Dispense in tight container (USP) C96-16 (Rev. 3/96)

Shown in Product Identification Guide, page 309

ESTRADERM® ℞

estradiol transdermal system
Continuous delivery for twice-weekly application

Prescribing Information

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possible testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

There is no indication for estrogen therapy during pregnancy.

Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

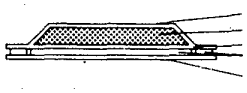
DESCRIPTION

Estraderm, estradiol transdermal system, is designed to release 17β-estradiol through a rate-limiting membrane continuously upon application to intact skin.

Two systems are available to provide nominal in vivo delivery of 0.05 or 0.1 mg of estradiol per day via skin of average permeability (interindividual variation in skin permeability is approximately 20%). Each corresponding system having an active surface area of 10 or 20 cm^2 contains 4 or 8 mg of estradiol USP and 0.3 or 0.6 mL of alcohol USP, respectively. The composition of the systems per unit area is identical.

Estradiol USP (17β-estradiol) is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3, 17β-diol.

The Estraderm system comprises four layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a transparent polyester film, (2) a drug reservoir of estradiol USP and alcohol USP gelled with hydroxypropyl cellulose, (3) an ethylene-vinyl acetate copolymer membrane, and (4) an adhesive formulation of light mineral oil and polyisobutylene. A protective liner (5) of siliconized polyethylene terephthalate film is attached to the adhesive surface and must be removed before the system can be used.



The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive. Alcohol is also released from the system during use.

CLINICAL PHARMACOLOGY

The Estraderm system releases estradiol, the major estrogenic hormone secreted by the human ovary. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor level.

Estraderm provides systemic estrogen replacement therapy. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and in the bone of women. Among numerous effects, estradiol is largely responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. By a direct action, it causes growth and development of the vagina, uterus, and fallopian tubes. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens contribute to the shaping of the skeleton, to the maintenance of tone and elasticity of urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of axillary and pubic hair, and to the pigmentation of the nipples and genitals.

Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy and affect the release of pituitary gonadotropins.

Loss of ovarian estradiol secretion after menopause can result in instability of thermoregulation, causing hot flushes associated with sleep disturbance and excessive sweating, and urogenital atrophy, causing dyspareunia and urinary incontinence. Estradiol replacement therapy alleviates many of these symptoms of estradiol deficiency in the menopausal woman.

Transdermal administration produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates, and requires smaller total doses than does oral therapy. Because estradiol has a short half-life (~1 hour), transdermal administration of estradiol allows a rapid decline in blood levels after an Estraderm system is removed, e.g., in a cycling regimen.

In a study using transdermally administered estradiol, 0.1 mg daily, plasma levels increased by 66 pg/mL, resulting in an average plasma level of 73 pg/mL. There were no significant increases in the concentration of renin substrate or other hepatic proteins (sex hormone-binding globulin, thyroxine-binding globulin, and corticosteroid-binding globulin).

Pharmacokinetics

Administration of Estraderm produces mean serum concentrations of estradiol comparable to those produced by a daily oral administration of estradiol at about 20 times the daily transdermal dose. In single-application studies in 14 postmenopausal women using Estraderm systems that provided 0.05 and 0.1 mg of exogenous estradiol per day, these systems produced increased blood levels within 4 hours and maintained respective mean serum estradiol concentrations of 32 and 67 pg/mL above baseline over the application period. At the same time, increases in estrone serum concentration averaged only 9 and 27 pg/mL above baseline, respectively. Serum concentrations of estradiol and estrone returned to preapplication levels within 24 hours after removal of the system. The estimated daily urinary output of estradiol conjugates increased 5 to 10 times the baseline values and returned to near baseline within 2 days after removal of the system.

By comparison, estradiol (2 mg/day) administered orally to postmenopausal women resulted in increases in mean serum concentration of 59 pg/mL of estradiol and 302 pg/mL of estrone above baseline on the third consecutive day of dosing. Urinary output of estradiol conjugates after oral administration increased to about 100 times the baseline values and did not approach baseline until 7–8 days after the last dose.

In a 3-week multiple-application study of 14 postmenopausal women in which Estraderm 0.05 was applied twice weekly, the mean increments in steady-state serum concentration were 30 pg/mL for estradiol and 12 pg/mL for estrone. Urinary output of estradiol conjugates returned to baseline within 3 days after removal of the last (6th) system, indicating little or no estrogen accumulation in the body.

INDICATIONS AND USAGE

Estraderm® (estradiol transdermal system) is indicated in the following:

1. Treatment of moderate-to-severe vasomotor symptoms associated with menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression that might occur during menopause, and they should not be used to treat these conditions.
2. Treatment of atrophic vaginitis and kraurosis vulvae.
3. Treatment of atrophic urethritis.
4. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
5. Prevention of osteoporosis (loss of bone mass). The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Estrogen replacement therapy is the most effective single modality for the prevention of postmenopausal osteoporosis in women. Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-controlled studies have shown an approximately 60% reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen prevents further loss of bone mass for as long as treatment is continued. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period. A well-controlled, double-blind, prospective trial conducted at the Mayo Clinic has demonstrated that treatment with Estraderm prevents bone loss in postmenopausal women at a dosage of 0.05 mg/day.

Treatment with Estraderm 0.05 mg showed full maintenance of bone density with a slight (0.8%), but not significant, increase. Placebo treatment resulted in a significant loss of more than 6% below baseline vertebral bone mass. Patients using either Estraderm 0.1 or 0.05 mg had significantly greater bone densities than those using placebo.

Women are at higher risk than men because they have less bone mass, and for several years following natural or induced menopause, the rate of bone mass decline is accelerated. Early menopause is one of the strongest predictors for the development of osteoporosis. In addition, other factors affecting the skeleton that are associated with osteoporosis include race (white and Asian women are at higher risk than black women); genetic factors (small build, family history); endocrine factors (nulliparity, thyrotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperprolactinemia, Type I diabetes); life-style (cigarette smoking, alcohol abuse, sedentary habits); and nutrition (below-average body weight, dietary calcium intake). Calcium deficiency has been implicated in the pathogenesis of the disease. Therefore, when not contraindicated, it is recommended that postmenopausal women receive calcium supplementation.

Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established.

CONTRAINDICATIONS

Patients with known hypersensitivity to any of the components of the therapeutic system should not use Estraderm.

Estrogens should not be used in women with any of the following conditions:

1. Known or suspected pregnancy (see Boxed Warning). Estrogen may cause fetal harm when administered to a pregnant woman.
2. Known or suspected cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.

WARNINGS

1. *Induction of malignant neoplasms.* Some studies have suggested a possible increased incidence of breast cancer in those women taking estrogen therapy at higher doses or for prolonged periods of time. The majority of studies, however, have not shown an association with the usual doses used for estrogen replacement therapy. Women on this therapy should have regular breast examinations and should be instructed in breast self-examination. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use with increased risks of 15- to 24-fold for 5 to 10 years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study, a significant decrease in the incidence of endometrial cancer occurred 6 months after estrogen withdrawal. Concurrent progestin therapy may offset this risk, but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders. In female offspring, there is an increased risk of vaginal adenosis, squamous cell dysplasia of the cervix, and clear cell vaginal cancer later in life; in males, urogenital and possibly testicular abnormalities. Although some of these changes are benign, it is not known whether they are precursors of malignancy.

2. *Gallbladder disease.* Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in postmenopausal women receiving oral estrogen replacement therapy, similar to the 2-fold increase previously noted in users of oral contraceptives.

3. *Cardiovascular disease.* Large doses of oral estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. It cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

4. *Elevated blood pressure.* Occasional blood pressure increases during postmenopausal estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. Postmenopausal estrogen use does not increase the risk of stroke; nonetheless, blood pressure should be monitored at regular intervals with estrogen use, especially if high doses are used. Ethinyl estradiol and conjugated estrogens have been shown to increase renin substrate. In contrast to these oral estrogens, transdermally administered estradiol does not affect renin substrate.

5. *Hypercalcemia.* Administration of estrogen may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium levels.

PRECAUTIONS

General

1. *Addition of a progestin.* Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphologic and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes. There are possible additional risks that may be associated with the use of progestins in estrogen replacement regimens. These include (1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL), which could diminish the purported cardioprotective effect of estrogen therapy (see PRECAUTIONS, below); (2) impairment of glucose tolerance; and (3) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiologic data are available to address this point (see PRECAUTIONS, below). The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

2. *Cardiovascular risk.* A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years, many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy *without added progestins* and a decrease in cardiovascular disease in women. Although most of the observational studies that assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

1. Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. The apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the possibility that healthier women were selected for estrogen therapy. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.
2. Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels.
3. While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS, above).

Because relatively long-term use of estrogens by women with uteri has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale, randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

3. *Physical examination.* A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than 1 year without another physical examination being performed.

4. *Hypercoagulability.* Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low-dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (primarily of users of conjugated estrogens) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease. Women on estrogen replacement therapy have not been reported to have an increased risk of thrombophlebitis and/or thromboembolic disease. However, there is insufficient information regarding women who have had previous thromboembolic disease.

5. *Familial hyperlipoproteinemia.* Estrogen therapy may be associated with massive elevations of plasma triglycerides, leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

6. *Fluid retention.* Because estrogens may cause some degree of fluid retention, conditions that might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

7. *Uterine bleeding and mastodynia.* Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

8. *Impaired liver function.* Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

Information for the Patient

See text of Patient Package Insert, which appears after the HOW SUPPLIED section.

Laboratory Tests

Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable. For prevention and treatment of osteoporosis, however, see DOSAGE AND ADMINISTRATION. Tests used to measure adequacy of estrogen replacement therapy include serum estrone and estradiol levels and suppression of serum gonadotropin levels.

Drug/Laboratory Test Interactions

Some of these drug/laboratory test interactions have been observed only with estrogen-progestin combinations (oral contraceptives):

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by T_4 levels determined either by column or by radioimmunoassay. Free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 and free T_3 concentrations are unaltered.
3. Other binding proteins may be elevated in serum, i.e., corticosteroid-binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1–antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.
7. Reduced serum folate concentration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, testis, and liver (see CONTRAINDICATIONS and WARNINGS).

Pregnancy Category X

Estrogens should not be used during pregnancy (see CONTRAINDICATIONS and Boxed Warning).

Nursing Mothers

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS

(See WARNINGS regarding induction of neoplasia, adverse effects on the fetus, gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia.)

The most commonly reported adverse reaction to Estraderm in clinical trials was redness and irritation at the application site. This occurred in about 17% of the women treated and caused approximately 2% to discontinue therapy. Reports of rash have been rare. There have also been rare reports of severe systemic allergic reactions.

The following additional adverse reactions have been reported with estrogen therapy:

1. *Genitourinary system.* Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; increase in size of uterine leiomyomata; vaginal candidiasis; change in amount of cervical secretion.

Continued on next page

CibaGeneva—Cont.

2. *Breasts.* Tenderness, enlargement.
3. *Gastrointestinal.* Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; gallbladder disease.
4. *Skin.* Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.
5. *Eyes.* Steepening of corneal curvature; intolerance to contact lenses.
6. *CNS.* Headache, migraine, dizziness; mental depression; chorea.
7. *Miscellaneous.* Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawl beeding may occur in females.

DOSAGE AND ADMINISTRATION

The adhesive side of the Estraderm system should be placed on a clean, dry area of the skin on the trunk of the body (including the buttocks and abdomen). The site selected should be one that is not exposed to sunlight. *Estraderm should not be applied to the breasts.* The Estraderm system should be replaced twice weekly. The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the unlikely event that a system should fall off, the same system may be reapplied. If necessary, a new system may be applied. In either case, the original treatment schedule should be continued.

Initiation of Therapy

Estraderm is currently available in two dosage forms—0.05 mg and 0.1 mg. For treatment of moderate-to-severe vasomotor symptoms, atrophic vaginitis, and atrophic urethritis associated with menopause, initiate therapy with Estraderm 0.05 applied to the skin twice weekly. The lowest dose that will control symptoms should be chosen, and medication should be discontinued as promptly as possible. Attempts to discontinue or taper medication given only for these menopausal symptoms should be made at 3-month to 6-month intervals.

Prophylactic therapy with Estraderm to prevent postmenopausal bone loss should be initiated with the 0.05 mg/day dosage as soon as possible after menopause. The dosage may be adjusted if necessary. Discontinuation of estrogen replacement therapy may reestablish bone loss at a rate comparable to the immediate postmenopausal period.

In women not currently taking oral estrogens, treatment with Estraderm may be initiated at once. In women who are currently taking oral estrogen, treatment with Estraderm should be initiated 1 week after withdrawal of oral hormone replacement therapy, or sooner if menopausal symptoms reappear in less than 1 week.

Therapeutic Regimen

Estraderm therapy may be given continuously in patients who do not have an intact uterus. In those patients with an intact uterus, Estraderm may be given on a cyclic schedule (e.g., 3 weeks on drug followed by 1 week off drug).

HOW SUPPLIED

Estraderm estradiol transdermal system 0.05 mg/day—each 10 cm^2 system contains 4 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 Systems ..... NDC 0083-2310-08
Carton of 6 Patient Calendar Packs of 8 Systems ..... NDC 0083-2310-62
Carton of 1 Patient Calendar Pack of 24 Systems ..... NDC 0083-2310-24

Estraderm estradiol transdermal system 0.1 mg/day—each 20 cm^2 system contains 8 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 Systems ..... NDC 0083-2320-08
Carton of 6 Patient Calendar Packs of 8 Systems ..... NDC 0083-2320-62
Carton of 1 Patient Calendar Pack of 24 Systems ..... NDC 0083-2320-24

*See DESCRIPTION.

Do not store above 86°F (30°C).

Do not store unpouched. Apply immediately upon removal from the protective pouch.

C95-43 (Rev. 10/95)

Information for the Patient

ESTRADERM® ℞

Generic name: estradiol transdermal system pronounced ess-tra-DYE-al)

1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE").

If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

INTRODUCTION

Your doctor has prescribed Estraderm for the treatment of your menopausal symptoms and/or to prevent osteoporosis. During menopause, production of estrogen hormones by your body decreases well below the amounts normally produced during your fertile years. In many women, this decrease in estrogen production causes uncomfortable symptoms, most noticeably, hot flushes and sleep disturbance. Estrogens can be given to reduce or eliminate these symptoms and/or to prevent osteoporosis.

The Estraderm system that your doctor has prescribed for you releases small amounts of estradiol through the skin in a continuous way. Estradiol is the same hormone that your ovaries produce abundantly before menopause. Your doctor will prescribe the lowest dose you require, depending upon your individual response. The dose is adjusted by the size of the Estraderm system used; the systems are available in two sizes. The length of treatment will depend on the reason for use.

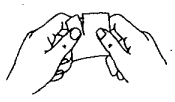
INFORMATION ABOUT ESTRADERM

How Estraderm Works

Estraderm contains estradiol. When applied to the skin as directed below, the Estraderm system releases estradiol, which flows through the skin into the bloodstream.

How and Where to Apply Estraderm

Each Estraderm system is individually sealed in a protective pouch. Tear open this pouch at the indentation (do not use scissors) and remove the system. Bubbles in the system are normal.



A stiff protective liner covers the adhesive side of the system—the side that will be placed against your skin. This liner must be removed before applying the system. Slide the protective liner sideways between your thumb and index finger. Then hold the system at one edge. Remove the protective liner and discard it. Try to avoid touching the adhesive.

Apply the adhesive side of the system to a clean, dry area of the skin on the trunk of the body (including the buttocks and abdomen).

The site selected should be one that is not exposed to sunlight. Some women may find that it is more comfortable to wear Estraderm on the buttocks. *Do not apply Estraderm to your breasts.* The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub the system off. Apply the system immediately after opening the pouch and removing the protective liner. Press the system firmly in place with the palm of your hand for about 10 seconds, making sure there is good contact, especially around the edges.

The Estraderm system should be worn continuously until it is time to replace it with a new system. You may wish to experiment with different locations when applying a new system, to find ones that are most comfortable for you and where clothing will not rub on the system.

When to Apply Estraderm

The Estraderm system should be replaced twice weekly. Your Estraderm package contains a calendar checklist on the back to help you remember a schedule. Mark the 2-day schedule you plan to follow. Always change the system on the 2 days of the week you have marked.

When changing the system, remove the used Estraderm and discard it. Any adhesive that might remain on your skin can be easily rubbed off. Then place the new Estraderm on a different skin site. (The same skin site should not be used again for at least 1 week after removal of the system.)

Please note: Contact with water when you are bathing, swimming, or showering will not affect the system. In the unlikely event that a system should fall off, put this same system back on and continue to follow your original treatment schedule. If necessary, you may apply a new system but continue to follow your original schedule.

Benefits of Treatment With Estraderm

Regular use of Estraderm twice weekly offers relief of moderate-to-severe symptoms of menopause and has been shown to help prevent osteoporosis, which is a thinning of the bones that makes them more fragile. In the years following the menopause, unless estrogen therapy is taken regularly, your bones can rapidly lose strength, possibly leading to osteoporosis and bone fractures. Estraderm may prevent this bone loss and the development of osteoporosis and may help you to avoid fractures of your spine ("dowager's hump"), wrist, and hip later in life.

Small quantities of the naturally occurring hormone estradiol are absorbed through the skin from the Estraderm system, ensuring a continuous supply of circulating hormone in the body.

There is no medical evidence that the use of any estrogen during menopause will keep you feeling young, keep your skin soft, or relieve nervousness.

USES OF ESTROGEN

To reduce moderate-to-severe menopausal symptoms. Estrogens are hormones produced by the ovaries. The decrease in the amount of estrogen that occurs in all women, usually between ages 45 and 55, causes the menopause. Sometimes the ovaries are removed by an operation, causing "surgical menopause." When the amount of estrogen begins to decrease, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest or sudden intense episodes of heat and sweating ("hot flashes"). The use of drugs containing estrogens can help the body adjust to lower estrogen levels.

Some women have only mild menopausal symptoms, or none at all, and do not need estrogen therapy for these particular symptoms. Other women may need estrogens for a few months while their bodies adjust to lower estrogen levels. For the treatment of menopausal symptoms only, most women need estrogen replacement therapy for no longer than 6 months. The prevention of osteoporosis may require longer-term therapy.

To prevent osteoporosis (brittle bones). After age 40, and especially after menopause, women begin to lose bone more rapidly, and some women develop osteoporosis. This thinning of the bones makes the bones weaker and more likely to break, often leading to fractures of the spine, hip, and wrist. Taking estrogens after the menopause slows down or halts bone loss and may prevent bones from breaking. Rapid loss of bone may begin soon after estrogen therapy is discontinued. Eating foods that are high in calcium (such as milk products) or taking calcium supplements and certain types of exercise may also help prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these life-style changes with your doctor to find out if they are safe for you. Since estrogen use is associated with some risk, its use in the prevention of osteoporosis should be confined to women who appear to be susceptible to this condition. The following characteristics are often present in women who are likely to develop osteoporosis: early menopause; white or Asian race; a family history of osteoporosis in a mother, sister, or aunt; slight build; cigarette smoking; alcohol abuse; or sedentary life-style.

Women who had their menopause by the surgical removal of their ovaries at a relatively young age may be good candidates for Estraderm therapy to help prevent osteoporosis.

To treat atrophic vaginitis (itching, burning, dryness in or around the vagina) *and atrophic urethritis* (which may cause difficulty or burning on urination).

WHEN ESTROGENS SHOULD NOT BE USED

During pregnancy. Although the possibility is fairly small, there is a greater risk of having a child born with a birth defect if you take estrogens during pregnancy. A male child may have an increased risk of developing abnormalities of the urinary system and sex organs. A female child may have an increased risk of developing cancer of the vagina or cervix in her teens or twenties. Estrogen is not effective in preventing miscarriage (abortion). In addition, estrogen should not be used after childbirth to prevent the breast from filling with milk, or while breast-feeding.

If you have undiagnosed vaginal bleeding. Unusual vaginal bleeding can be a warning sign of uterine cancer, especially if it happens after menopause. Your doctor must find out the proper treatment, if any. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.

If you have any circulation problems. Estrogen therapy should be used only after consultation with your doctor and only in recommended doses. Patients with a tendency for abnormal blood clotting should avoid estrogen use (see DANGERS OF ESTROGENS).

If you have had cancer. Since estrogens increase the risk of certain cancers, you should not take estrogens if you have ever had cancer of the breast or uterus.

When they are ineffective. Sometimes women experience nervous symptoms or depression during menopause. There is no evidence that estrogens are effective for such symptoms. You may have heard that taking estrogens for long periods (years) after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims, and such long-term treatment may carry serious risks.

DANGERS OF ESTROGENS

Cancer of the uterus. The risk of cancer of the uterus increases the longer estrogens are used and when larger doses are taken. One study showed that when estrogens are discontinued, this increased risk of cancer seems to fall off quickly. Three other studies showed that the risk for uterine cancer stayed high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk, *it is important to take the lowest dose of estrogen that will control your symptoms and to take it only as long as you need it.* Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (see OTHER INFORMATION).

If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.

Cancer of the breast. The majority of studies have shown no association between the usual doses used for estrogen replacement therapy and breast cancer. Some studies have suggested a possible increased incidence of breast cancer in those women taking estrogens for prolonged periods of time and especially if higher doses are used.

Regular breast examinations by a health professional and monthly self-examination are recommended for women receiving estrogen therapy, as they are for all women.

Gallbladder disease. Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

Abnormal blood clotting. Taking estrogens may increase the risk of blood clots. These clots can cause a stroke, heart attack, or pulmonary embolus, any of which may be fatal. However, most studies of low-dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

- Nausea and vomiting.
- Breast tenderness or enlargement.
- Enlargement of benign tumors of the uterus.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face.
- Skin irritation, redness, or rash may occur at the site of Estraderm application.

REDUCING RISK OF ESTROGEN USE

If you decide to take estrogen replacement therapy, you can reduce your risks by carefully monitoring your treatment.

See your doctor regularly. While you are taking estrogens, it is important that you visit your doctor at least once a year for a physical examination. If members of your family have had breast cancer or if you have ever had breast nodules or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.

Reevaluate your need for estrogens. You and your doctor should reevaluate your need for estrogens at least every 6 months.

Be alert for signs of trouble. Report these or any other unusual side effects to your doctor immediately:

- Abnormal bleeding from the vagina.
- Pains in the calves or chest, a sudden shortness of breath, or coughing blood (indicating possible clots in the legs, heart, or lungs).
- Severe headache, dizziness, faintness, or changes in vision, indicating possible clots in the brain or eye.
- Breast lumps.
- Yellowing of the skin.
- Pain, swelling, or tenderness in the abdomen.
- Skin irritation, redness, or rash.

OTHER INFORMATION

If your uterus has not been removed, your doctor may choose to prescribe a progestin, a different hormonal drug, to be used in association with estrogen treatment. Progestins lower the risk of developing endometrial hyperplasia, a possible precancerous condition of the uterine lining, which may occur while using estrogens. There are possible additional risks that may be associated with the inclusion of a progestin in estrogen treatment. The possible risks include unfavorable effects on blood fats and sugars, as well as a possible further increase in breast cancer risk that may be associated with long-term estrogen use.

Some research has suggested that estrogens taken *without progestins* may protect women against developing heart disease. However, this effect of estrogens is not certain.

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment, as they affect you personally.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about the amounts recommended.

Keep this and all other drugs out of the reach of children. In case of overdose, remove the Estraderm system and call your doctor, hospital, or poison control center immediately.

This leaflet provides the most important information about estrogens. If you want to read more, ask your doctor or pharmacist to let you read the professional labeling.

C95-44 (Rev. 10/95)
C95-43/C95-44 (Rev. 10/95)

Ciba-Geigy Corporation
Pharmaceuticals Division
Summit, New Jersey 07901

Shown in Product Identification Guide, page 309

ISMELIN® sulfate ℞
[*iz'mel-lin*]
guanethidine monosulfate USP
Tablets

DESCRIPTION

Ismelin, guanethidine monosulfate USP, is an antihypertensive, available as tablets of 10 mg and 25 mg for oral administration. Each 10-mg and 25-mg tablet contains guanethidine monosulfate USP equivalent to 10 mg and 25 mg of guanethidine sulfate, USP. Its chemical name is [2-(hexahydro-1(2*H*)-azocinyl)ethyl]guanidine sulfate 1:1.

Guanethidine monosulfate USP is a white to off-white crystalline powder with a molecular weight of 296.38. It is very soluble in water, sparingly soluble in alcohol, and practically insoluble in chloroform.

Inactive ingredients: Calcium stearate, colloidal silicon dioxide, D&C Yellow No. 10 (10-mg tablets), lactose, starch, stearic acid, and sucrose.

CLINICAL PHARMACOLOGY

Ismelin acts at the sympathetic neuroeffector junction by inhibiting or interfering with the release and/or distribution of the chemical mediator (presumably the catecholamine norepinephrine), rather than acting at the effector cell by inhibiting the association of the transmitter with its receptors. In contrast to ganglionic blocking agents, Ismelin suppresses equally the responses mediated by alpha- and beta-adrenergic receptors but does not produce parasympathetic blockade. Since sympathetic blockade results in modest decreases in peripheral resistance and cardiac output, Ismelin lowers blood pressure in the supine position. It further reduces blood pressure by decreasing the degree of vasoconstriction that normally results from reflex sympathetic nervous activity upon assumption of the upright posture, thus reducing venous return and cardiac output more. The inhibition of sympathetic venoconstrictive mechanisms results in venous pooling of blood. Therefore, the effect of Ismelin is especially pronounced when the patient is standing. Both the systolic and diastolic pressures are reduced.

Other actions at the sympathetic nerve terminal include depletion of norepinephrine. Once it gains access to the neuron, Ismelin accumulates within the intraneuronal storage vesicles and causes depletion of norepinephrine stores within the nerve terminal. Prolonged oral administration of Ismelin produces a denervation sensitivity of the neuroeffector junction, probably resulting from the chronic reduction in norepinephrine released by the sympathetic nerve endings. Systemic responses to catecholamines released from the adrenal medulla are not prevented and may even be augmented as a result of this denervation sensitivity. A paradoxical hypertensive crisis may occur if Ismelin is given to patients with pheochromocytoma or if norepinephrine is given to a patient receiving the drug.

Due to its poor lipid solubility, Ismelin does not readily cross the blood-brain barrier. In contrast to most neural blocking agents, Ismelin does not appear to suppress plasma renin activity in many patients.

Pharmacokinetics

The pharmacokinetics of Ismelin are complex. The amount of drug in plasma and in urine is linearly related to dose, although large differences occur between individuals because of variation in absorption and metabolism. Adrenergic blockade occurs with a minimum concentration in plasma of 8 ng/ml; this concentration is achieved in different individuals with dosages of 10–50 mg/day at steady state. Ismelin is eliminated slowly because of extensive tissue binding. After chronic oral administration, the initial phase of elimination with a half-life of 1.5 days is followed by a second phase of elimination with a half-life of 4–8 days. The renal clearance of Ismelin is 56 ml/min. Ismelin is converted by the liver to three metabolites, which are excreted in the urine. The metabolites are pharmacologically less active than Ismelin.

INDICATIONS AND USAGE

Ismelin is indicated for the treatment of moderate and severe hypertension, either alone or as an adjunct, and for the treatment of renal hypertension, including that secondary to pyelonephritis, renal amyloidosis, and renal artery stenosis.

CONTRAINDICATIONS

Known or suspected pheochromocytoma; hypersensitivity; frank congestive heart failure not due to hypertension; use of monoamine oxidase (MAO) inhibitors.

WARNINGS

Ismelin is a potent drug and its use can lead to disturbing and serious clinical problems. Before prescribing, physicians should familiarize themselves with the details of its use and warn patients not to deviate from instructions.

> Orthostatic hypotension can occur frequently, and patients should be properly instructed about this potential hazard. Fainting spells may occur unless the patient is forewarned to sit or lie down with the onset of dizziness or weakness. Postural hypotension is most marked in the morning and is accentuated by hot weather, alcohol, or exercise. Dizziness or weakness may be particularly bothersome during the initial period of dosage adjustment and with postural changes, such as arising in the morning. The potential occurrence of these symptoms may require alteration of previous daily activity. The patient should be cautioned to avoid sudden or prolonged standing or exercise while taking the drug.

Inhibition of ejaculation has been reported in animals (see **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**) as well as in men given Ismelin. This effect, which results from the sympathetic blockade caused by the drug's action, is reversible after Ismelin has been discontinued for several weeks. The drug does not cause parasympathetic blockade, and erectile potency is usually retained during administration of Ismelin. The possible occurrence of inhibition of ejaculation should be kept in mind when considering the use of guanethidine in men of reproductive age.

If possible, therapy should be withdrawn 2 weeks prior to surgery to reduce the possibility of vascular collapse and cardiac arrest during anesthesia. If emergency surgery is indicated, preanesthetic and anesthetic agents should be administered cautiously in reduced dosage. Oxygen, atropine, vasopressors, and adequate solutions for volume replacement should be ready for immediate use to counteract vascular collapse in the surgical patient. Vasopressors should be used only with extreme caution, since Ismelin augments responsiveness to exogenously administered norepinephrine and vasopressors; specifically, blood pressure may rise and cardiac arrhythmias may be produced.

PRECAUTIONS

General

Dosage requirements may he reduced in the presence of fever.

Special care should be exercised when treating patients with a history of bronchial asthma; asthmatic patients are more apt to be hypersensitive to catecholamine depletion, and their condition may be aggravated.

The effects of Ismelin are cumulative over long periods; initial doses should be small and increased gradually in small increments.

Ismelin should be used very cautiously in hypertensive patients with renal disease and nitrogen retention or rising BUN levels, since decreased blood pressure may further compromise renal function, coronary insufficiency or recent

Continued on next page

CibaGeneva—Cont.

Children have been reported to be more sensitive than adults to an acute overdosage of imipramine pamoate. An acute overdose of any amount in infants or young children, especially, must be considered serious and potentially fatal.

Manifestations

These may vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the interval between drug ingestion and the start of treatment. Critical manifestations of overdose include cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic toxicity.

Other CNS manifestations may include drowsiness, stupor, ataxia, restlessness, agitation, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements.

Cardiac abnormalities may include tachycardia, and signs of congestive failure. Respiratory depression, cyanosis, shock, vomiting, hyperpyrexia, mydriasis, and diaphoresis may also be present.

Management

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line, and initiate gastric decontamination. A minimum of 6 hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination: All patients suspected of tricyclic overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular: A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and the hyperventilation (as needed) should be instituted for patients with dysrhythmias and/or QRS widening. A pH > 7.60 or a Pco_2 < 20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic poisoning.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase.

Psychiatric referral may be appropriate.

Pediatric Management: The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

HOW SUPPLIED

Capsules 75 mg—coral (imprinted black Geigy 20) equivalent to 75 mg imipramine hydrochloride

Bottles of 30	NDC 0028-0020-26
Bottles of 100	NDC 0028-0020-01

Capsules 100 mg—dark yellow/coral (imprinted black Geigy 40) equivalent to 100 mg imipramine hydrochloride

Bottles of 30	NDC 0028-0040-26
Bottles of 100	NDC 0028-0040-01

Capsules 125 mg—ivory/coral (imprinted black Geigy 45) equivalent to 125 mg imipramine hydrochloride

Bottles of 30	NDC 0028-0045-26
Bottles of 100	NDC 0028-0045-01

Capsules 150 mg—coral (imprinted black Geigy 22) equivalent to 150 mg imipramine hydrochloride

Bottles of 30	NDC 0028-0022-26
Bottles of 100	NDC 0028-0022-01

Do not store above 86°F (30°C).

Dispense in tight container (USP).

ANIMAL PHARMACOLOGY & TOXICOLOGY

A. *Acute:* Oral LD_{50}:

Mouse	2185 mg/kg
Rat (F)	1142 mg/kg
(M)	1807 mg/kg
Rabbit	1016 mg/kg
Dog	693 mg/kg (Emesis ED_{50})

B. *Subacute:*

Two three-month studies in dogs gave evidence of an adverse drug effect on the testes, but only at the highest dose level employed, i.e., 90 mg/kg (10 times the maximum human dose). Depending on the histological section of the testes examined, the findings consisted of a range of degenerative changes up to and including complete atrophy of the seminiferous tubules, with spermatogenesis usually arrested.

Human studies show no definitive effect on sperm count, sperm motility, sperm morphology or volume of ejaculate.

Rat

One three-month study was done in rats at dosage levels comparable to those of the dog studies. No adverse drug effect on the testes was noted in this study, as confirmed by histological examination.

C. *Reproduction/Teratogenic:*

Oral: Imipramine pamoate was fed to male and female albino rats for 28 weeks through two breeding cycles at dose levels of 15 mg/kg/day and 40 mg/kg/day (equivalent to $2^1/_2$ and 7 times the maximum human dose).

No abnormalities which could be related to drug administration were noted in gross inspection. Autopsies performed on pups from the second breeding likewise revealed no pathological changes in organs or tissues; however, a decrease in mean litter size from both matings was noted in the drug-treated groups and significant growth suppression occurred in the nursing pups of both sexes in the high group as well as in the females of the low-level group. Finally, the lactation index (pups weaned divided by number left to nurse) was significantly lower in the second litter of the high-level group.

C96-4 (Rev. 1/96)

Ciba-Geigy Corporation
Pharmaceuticals Division
Summit, NJ 07901

Shown in Product Identification Guide, page 309

TRANSDERM-NITRO®

℞

[trans'derm nye'trow]

nitroglycerin

Transdermal Therapeutic System

Prescribing Information

DESCRIPTION

Nitroglycerin is 1,2,3-propanetriol, trinitrate, an organic nitrate whose molecular weight is 227.09. The organic nitrates are vasodilators, active on both arteries and veins.

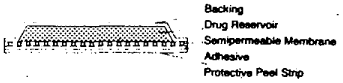
The Transderm-Nitro (nitroglycerin) transdermal system is a flat unit designed to provide continuous controlled release of nitroglycerin through intact skin.

The rate of release of nitroglycerin is linearly dependent upon the area of the applied system; each cm^2 of applied system delivers approximately 0.02 mg of nitroglycerin per hour. Thus, the 5-, 10-, 20-, and 30-cm^2 systems deliver approximately 0.1, 0.2, 0.4, and 0.6 mg of nitroglycerin per hour, respectively.

The remainder of the nitroglycerin in each system serves as a reservoir and is not delivered in normal use. After 12 hours, for example, each system has delivered 10% of its original content of nitroglycerin.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface towards the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene-vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:



CLINICAL PHARMACOLOGY

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle, and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates had been absent from the body for several hours was their antianginal efficacy restored.

Pharmacokinetics

The volume of distribution of nitroglycerin is about 3L/kg, and nitroglycerin is cleared from this volume at extremely rapid rates, with a resulting serum half-life of about 3 minutes. The observed clearance rates (close to 1L/kg/min) greatly exceed hepatic blood flow, known sites of extrahepatic metabolism include red blood cells and vascular walls.

The first products in the metabolism of nitroglycerin are inorganic nitrate and the 1,2- and 1,3-dinitroglycerols. The dinitrates are less effective vasodilators than nitroglycerin, but they are longer-lived in the serum, and their net contribution to the overall effect of chronic nitroglycerin regimens is not known. The dinitrates are further metabolized to (non-vasoactive) mononitrates and, ultimately, to glycerol and carbon dioxide.

To avoid development of tolerance to nitroglycerin, drug-free intervals of 10–12 hours are known to be sufficient; shorter intervals have not been well studied. In one well-controlled clinical trial, subjects receiving nitroglycerin appeared to exhibit a rebound or withdrawal effect, so that their exercise tolerance at the end of the daily drug-free interval was *less* than that exhibited by the parallel group receiving placebo.

In healthy volunteers, steady-state plasma concentrations of nitroglycerin are reached by about two hours after application of a patch and are maintained for the duration of wearing the system (observations have been limited to 24 hours). Upon removal of the patch, the plasma concentration declines with a half-life of about an hour.

Clinical Trials

Regimens in which nitroglycerin patches were worn for 12 hours daily have been studied in well-controlled trials up to 4 weeks in duration. Starting about 2 hours after application and continuing until 10–12 hours after application, patches that deliver at least 0.4 mg of nitroglycerin per hour have consistently demonstrated greater antianginal activity than placebo. Lower-dose patches have not been as well studied, but in one large, well-controlled trial in which higher-dose patches were also studied, patches delivering 0.2 mg/hr had significantly less antianginal activity than placebo.

It is reasonable to believe that the rate of nitroglycerin absorption from patches may vary with the site of application, but this relationship has not been adequately studied.

The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

INDICATIONS AND USAGE

Transdermal nitroglycerin is indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute attack.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

WARNINGS

The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a Transderm-Nitro patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS

General

Severe hypotension, particularly with upright posture, may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be

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accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10–12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients demonstrated decreased exercise tolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is unknown.

Information for Patients

Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets.

A patient leaflet is supplied with the systems.

Drug Interactions

The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal carcinogenesis studies with topically applied nitroglycerin have not been performed.

Rats receiving up to 434 mg/kg/day of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes. At high dose, the incidences of hepatocellular carcinomas in both sexes were 52% vs. 0% in controls, and incidences of testicular tumors were 52% vs. 8% in controls. Lifetime dietary administration of up to 1058 mg/kg/day of nitroglycerin was not tumorigenic in mice.

Nitroglycerin was weakly mutagenic in Ames tests performed in two different laboratories. Nevertheless, there was not evidence of mutagenicity in an in vivo dominant lethal assay with male rats treated with doses up to about 363 mg/kg/day, p.o., or in in vitro cytogenetic tests in rat and dog tissues.

In a three-generation reproduction study, rats received dietary nitroglycerin at doses up to about 434 mg/kg/day for six months prior to mating of the F_0 generation with treatment continuing through successive F_1 and F_2 generations. The high dose was associated with decreased feed intake and body weight gain in both sexes at all matings. No specific effect on the fertility of the F_0 generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and aspermatogenesis in the high-dose males. In this three-generation study there was no clear evidence of teratogenicity.

Pregnancy Category C

Animal teratology studies have not been conducted with nitroglycerin transdermal systems. Teratology studies in rats and rabbits, however, were conducted with topically applied nitroglycerin ointment at doses up to 80 mg/kg/day and 240 mg/kg/day, respectively. No toxic effects on dams or fetuses were seen at any dose tested. There are no adequate and well-controlled studies in pregnant women. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Allergic reactions to nitroglycerin are also uncommon, and the great majority of those reported have been cases of contact dermatitis or fixed drug eruptions in patients receiving nitroglycerin in ointments or patches. There have been a few reports of genuine anaphylactoid reactions, and these reactions can probably occur in patients receiving nitroglycerin by any route.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see Overdosage).

Application-site irritation may occur but is rarely severe.

In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

	Placebo	Patch
Headache	18%	63%
Lightheadedness	4%	6%
Hypotension, and/or syncope	0%	4%
Increased angina	2%	2%

OVERDOSAGE

Hemodynamic Effects

The ill effects of nitroglycerin overdose are generally the result of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia

Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant ($\geq 10\%$) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2–4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1–2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

The suggested starting dose is between 0.2 mg/hr*, and 0.4 mg/hr*. Doses between 0.4 mg/hr* and 0.8 mg/hr* have shown continued effectiveness for 10–12 hours daily for at least one month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10–12 hours is sufficient (see CLINICAL PHARMACOLOGY). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12–14 hours and a daily patch-off period of 10–12 hours. Although some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e., complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

PATIENT INSTRUCTIONS FOR APPLICATION OF SYSTEM

A patient leaflet is supplied with each carton.

HOW SUPPLIED

Nitroglycerin Transdermal System 0.1 mg/hr-tan, round (imprinted Transderm-Nitro 0.1 mg/hr), supplied in a foil-lined pouch

30 Systems	NDC 57267-902-26
**30 Systems	NDC 57267-902-42
**100 Systems	NDC 57267-902-30

Nitroglycerin Transdermal System 0.2 mg/hr-tan, oblong (imprinted Transderm-Nitro 0.2 mg/hr), supplied in a foil-lined pouch

30 Systems	NDC 57267-905-26
**30 Systems	NDC 57267-905-42
**100 Systems	NDC 57267-905-30

Nitroglycerin Transdermal System 0.4 mg/hr-tan, oblong (imprinted Transderm-Nitro 0.4 mg/hr), supplied in a foil-lined pouch

30 Systems	NDC 57267-910-26
**30 Systems	NDC 57267-910-42
**100 Systems	NDC 57267-910-30

Nitroglycerin Transdermal System 0.6 mg/hr-tan, oblong (imprinted Transderm-Nitro 0.6 mg/hr), supplied in a foil-lined pouch

30 Systems	NDC 57267-915-26
**30 Systems	NDC 57267-915-42
**100 Systems	NDC 57267-915-30

Nitroglycerin Transdermal System 0.8 mg/hr-tan, round (imprinted Transderm-Nitro 0.8 mg/hr), supplied in a foil-lined pouch

30 Systems	NDC 57267-920-26
**30 Systems	NDC 57267-920-42

*Rated release in vivo. Release rates were formerly described in terms of drug delivered per 24 hours. In these terms, the supplied Transderm-Nitro systems would be rated at 2.5 mg/24 hr (0.1 mg/hr), 5 mg/24 hr (0.2 mg/hr), 10 mg/24 hr (0.4 mg/hr), 15 mg/24 hr (0.6 mg/hr), and 20 mg/24 hr (0.8 mg/hr).

**Institutional Pack

Do not store above 86°F (30°C).

Do not store unpouched. Apply immediately upon removal from the pouch.

C95–25 (Rev. 6/95)

How to use

TRANSDERM-NITRO®

nitroglycerin

Transdermal Therapeutic System

for the prevention of angina

Transderm-Nitro is easy to use—it has a clear plastic backing, and a special adhesive that keeps the system firmly in place.

Where to place Transderm-Nitro.

Select any area of skin on the body, EXCEPT the extremities below the knee or elbow. The chest is the preferred site. The area should be clean, dry, and hairless. If hair is likely to interfere with system adhesion or removal, it can be clipped, but not shaved. Take care to avoid areas with cuts or irritations. Do NOT apply the system immediately after showering or bathing. It is best to wait until you are certain the skin is completely dry.

How to apply Transderm-Nitro® nitroglycerin

1. Each Transderm-Nitro system is individually sealed in a protective pouch. Tear open this pouch at the indicated indentations. Carefully pick up the system lengthwise with the tab up, and the clear plastic backing facing you. You should be able to see the white cream containing ni-

Continued on next page

CibaGeneva—Cont.

troglycerin. (On very rare occasions, you may find a system without any white medication in it. Do not use it. Simply apply another system.)

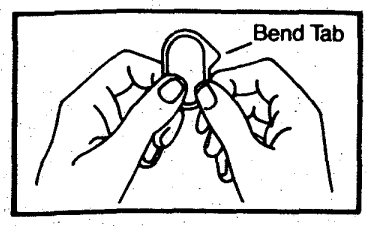


Figure A.

2. Firmly bend the tab forward with the thumb (Figure A). With both thumbs, begin to remove the clear plastic backing from the system at the tab (Figure B). Do not touch the inside of the exposed system, because the adhesive covers the entire surface.

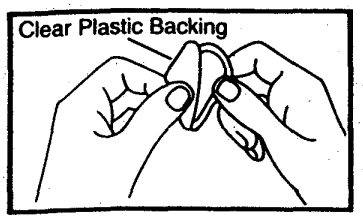


Figure B

3. Continue to remove the clear plastic backing slowly along the length of the system, allowing the system to rest on the outside of your fingers (Figure C).

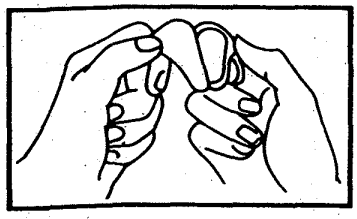


Figure C

4. Place the exposed, adhesive side of the system on the chosen skin site. Press firmly in place with the palm of your hand (Figure D). Once the system is in place, do not test the adhesion by pulling on it.

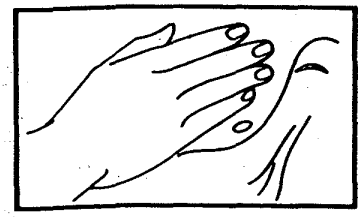


Figure D

When Transderm-Nitro is applied to your body, the nitroglycerin contained in the system begins to flow onto your skin through a unique rate-controlling membrane. This membrane allows the nitroglycerin to be released and available for absorption through your skin at a uniform rate.

5. At the time recommended by your doctor, remove and discard the system.
6. Place a new system on a different skin site, following Steps 1–4, according to your doctor's instructions.

Please note:
Contact with water, as in bathing, swimming, or showering will not affect the system. In the unlikely event that a system falls off, discard it and put a new one on a different skin site.

PRECAUTIONS

The most common side effect is headache, which often decreases as therapy is continued, but may require treatment with a mild analgesic. Although uncommon, faintness, flushing, and dizziness may occur, especially when suddenly rising from the recumbent (lying horizontal) position. If these symptoms occur, remove the system and notify your physician.

Skin irritation may occur. If it persists, consult your physician.

Keep these systems and all drugs out of the reach of children.

Important: Your doctor may decide to increase or decrease the size of the system, or prescribe a combination of systems, to suit your particular needs. The dose may vary depending on your individual response to the system.

This system is to be used for preventing angina, not for treating an acute attack.

DO NOT STORE ABOVE 86°F (30°C).

Do not store unpouched. Apply immediately upon removal from the protective pouch.

Dist. by:
Summit Pharmaceuticals
Ciba-Geigy Corp.
Summit, NJ 07901

C93-19 (Rev. 7/93)

Shown in Product Identification Guide, page 309

VIVELLE™

estradiol transdermal system
Continuous delivery for twice-weekly application

Prescribing Information

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

DESCRIPTION

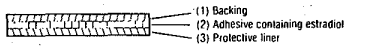
The Vivelle estradiol transdermal system contains estradiol in a multipolymeric adhesive. The system is designed to release 17β-estradiol continuously upon application to intact skin.

Four systems are available to provide nominal in vivo delivery of 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via skin of average permeability. Each corresponding system having an active surface area of 11.0, 14.5, 22.0, or 29.0 cm^2 contains 3.28, 4.33, 6.57, or 8.66 mg of estradiol USP, respectively. The composition of the systems per unit area is identical.

Estradiol USP (17β-estradiol) is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol.

The molecular formula of estradiol is $C_{18}H_{24}O_2$. The molecular weight is 272.39.

The Vivelle system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent flexible film consisting of an ethylene vinyl alcohol copolymer film, a polyurethane film, urethane polymer and epoxy resin, (2) an adhesive formulation containing estradiol, acrylic adhesive, polyisobutylene, ethylene vinyl acetate copolymer, 1,3 butylene glycol, styrene-butadiene rubber, oleic acid, lecithin, propylene glycol, bentonite, mineral oil, and dipropylene glycol, and (3) a polyester release liner that is attached to the adhesive surface and must be removed before the system can be used. [See Figure at top of next column.]



The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.

CLINICAL PHARMACOLOGY

The Vivelle system releases estradiol, the major estrogenic hormone secreted by the human ovary. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor level.

Vivelle provides systemic estrogen replacement therapy. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women. Among numerous effects, estradiol is largely responsible for the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, it causes growth and development of the vagina, uterus, and fallopian tubes. With other hormones, such as pituitary hormones and progesterone, it causes enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens contribute to the shaping of the skeleton, to the maintenance of tone and elasticity of urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of axillary and pubic hair, and pigmentation of the nipples and genitals.

Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins.

Loss of ovarian estradiol secretion after menopause can result in instability of thermoregulation, causing hot flushes associated with sleep disturbance and excessive sweating, and urogenital atrophy, causing dyspareunia and urinary incontinence. Estradiol replacement therapy alleviates many of these symptoms of estradiol deficiency in the menopausal woman.

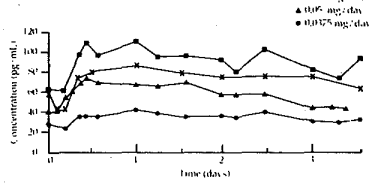
Pharmacokinetics

Transdermal administration produces therapeutic plasma levels of estradiol with lower circulating levels of estrone and estrone conjugates and requires smaller total doses than does oral therapy. Studies conducted with the Vivelle system show the drug has an apparent mean half-life of 4.4±2.3 hours.

In a multiple-dose study consisting of three consecutive patch applications of the Vivelle system, which was conducted in 17 healthy, postmenopausal women, blood levels of estradiol and estrone were compared following application of these units to sites on the abdomen and buttocks in a crossover fashion. Patches that deliver nominal estradiol doses of approximately 0.0375 mg/day and 0.1 mg/day were applied to abdominal application sites while the 0.1 mg/day doses were also applied to sites on the buttocks. These systems increased estradiol levels above baseline within 4 hours and maintained respective mean levels of 25 and 79 pg/mL above baseline following application to the abdomen; slightly higher mean levels of 88 pg/mL above baseline were observed following application to the buttocks. At the same time, increases in estrone plasma concentrations averaged about 12 and 50 pg/mL, respectively, following application to the abdomen and 61 pg/mL for the buttocks. While plasma concentrations of estradiol and estrone remained slightly above baseline at 12 hours following removal of the patches in this study, results from another study show these levels to return to baseline values within 24 hours following removal of the patches.

The graph illustrates the mean plasma concentrations of estradiol at steady-state during application of these patches at four different dosages.

Steady-State Estradiol Plasma Concentrations for Systems Applied to the Abdomen
Nonbaseline-corrected levels



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The corresponding pharmacokinetic parameters are summarized in the table below.

Steady-State Estradiol Pharmacokinetic Parameters for Systems Applied to the Abdomen (mean±standard deviation)
Nonbaseline-corrected data*

Dosage (mg/day)	C_{max}† (pg/mL)	C_{avg}‡ (pg/mL)	C_{min}(84 hr)§ (pg/mL)
0.0375	46±16	34±10	30±10
0.05	83±41	57±23#	41±11#
0.075	99±35	72±24	60±24
0.1	133±51	89±38	90±44
0.1¶	145±71	104±52	85±47

* Mean baseline estradiol concentration = 11.7 pg/mL
† Peak plasma concentration
‡ Average plasma concentration
§ Minimum plasma concentration at 84 hr
#Measured over 80 hr
¶ Applied to the buttocks

INDICATIONS AND USAGE

Vivelle™ (estradiol transdermal system) is indicated in the following:

1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression that might occur during menopause and they should not be used to treat these conditions.
2. Treatment of vulval and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

CONTRAINDICATIONS

Patients with known hypersensitivity to any of the components of the therapeutic system should not use Vivelle.

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see Boxed Warning). Estrogen may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast.
4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders.

WARNINGS

1. Induction of Malignant Neoplasms. Some studies have suggested a possible increased incidence of breast cancer in those women taking estrogen therapy at higher doses or for prolonged periods of time. The majority of studies, however, have not shown an association with the usual doses used for estrogen replacement therapy. Women on this therapy should have regular breast examinations and should be instructed in breast self-examination. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use with increased risks of 15- to 24-fold for 5 to 10 years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study, a significant decrease in the incidence of endometrial cancer occurred 6 months after estrogen withdrawal. Concurrent progestin therapy may offset this risk, but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders. In female offspring, there is an increased risk of vaginal adenosis, squamous cell dysplasia of the cervix, and clear cell vaginal cancer later in life; in males, urogenital and possibly testicular abnormalities. Although some of these changes are benign, it is not known whether they are precursors of malignancy.

2. Gallbladder Disease. Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in postmenopausal women receiving oral estrogen replacement therapy, similar to the 2-fold increase previously noted in users of oral contraceptives.

3. Cardiovascular Disease. Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

4. Elevated Blood Pressure. Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use, especially if high doses are used. Ethinyl estradiol and conjugated estrogens have been shown to increase renin substrate. In contrast to these oral estrogens, transdermally administered estradiol does not affect renin substrate.

5. Hypercalcemia. Administration of estrogen may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

General

1. Addition of a Progestin. Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lower incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphologic and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include

(1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL), which could diminish the purported cardioprotective effect of estrogen therapy (see PRECAUTIONS, below);

(2) impairment of glucose tolerance; and

(3) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiologic data are available to address this point (see PRECAUTIONS, below).

The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

2. Cardiovascular Risk. A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years, many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy *without added progestins* and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

(1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

(2) Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels.

(3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiologic evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS, above).

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

3. Physical Examination. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than 1 year without reexamining the patient.

4. Hypercoagulability. Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low-dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (primarily of users of conjugated estrogens) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.

5. Familial Hyperlipoproteinemia. Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

6. Fluid Retention. Because estrogens may cause some degree of fluid retention, conditions that might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

7. Uterine Bleeding and Mastodynia. Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

8. Impaired Liver Function. Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

Information for the Patient

See text of Patient Package Insert, which appears after the HOW SUPPLIED section.

Laboratory Tests

Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable.

Drug/Laboratory Test Interactions

Some of these drug/laboratory test interactions have been observed only with estrogen-progestin combinations (oral contraceptives):

1. Accelerated prothrombin time, partial thromboplastin time; and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex; and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.
3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL_2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.
7. Reduced serum folate concentration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, testis, and liver (see CONTRAINDICATIONS and WARNINGS).

Pregnancy Category X

Estrogens should not be used during pregnancy (see CONTRAINDICATIONS and Boxed Warning).

Nursing Mothers

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

ADVERSE REACTIONS

See WARNINGS and Boxed Warning regarding the potential adverse effects on the fetus, the induction of malignant neoplasms, gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia.

The most commonly reported systemic adverse event to the Vivelle system in controlled clinical trials was headache. This occurred in approximately 36% of patients treated with

Continued on next page

CibaGeneva—Cont.

active systems and in 30% of patients treated with placebo. The most common topical adverse events in these trials were erythema and pruritus at the application site. Most cases were considered mild. Fewer than 5% of patients on active drug at the final visit of the study had reactions of greater than mild intensity. Rash was reported rarely in these trials. Two patients out of 356 were discontinued from the trials due to skin irritation/erythema.

The following additional adverse reactions have been reported with estrogen therapy:

1. Genitourinary System. Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting; increase in size of uterine leiomyomata; vaginal candidiasis; change in amount of cervical secretion.

2. Breasts. Tenderness, enlargement.

3. Gastrointestinal. Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; gallbladder disease.

4. Skin. Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.

5. Eyes. Steepening of corneal curvature; intolerance to contact lenses.

6. Central Nervous System. Headache, migraine, dizziness; mental depression; chorea.

7. Miscellaneous. Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

The adhesive side of the Vivelle system should be placed on a clean, dry area of the skin on the trunk of the body (including the buttocks and abdomen). *Vivelle should not be applied to the breasts.* The Vivelle system should be replaced twice weekly. The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the unlikely event that a system should fall off, the same system may be reapplied. If necessary, a new system may be applied. In either case, the original treatment schedule should be continued.

Initiation of Therapy

For treatment of moderate-to-severe vasomotor symptoms and vulval and vaginal atrophy associated with the menopause, start therapy with the Vivelle estradiol transdermal system 0.05 mg/day applied to the skin twice weekly. In order to use the lowest dosage necessary for the control of symptoms, decisions to increase dosage should not be made until after the first month of therapy. Some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy. Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

In women not currently taking oral estrogens or in women switching from another estradiol transdermal therapy, treatment with the Vivelle estradiol transdermal system may be initiated at once. In women who are currently taking oral estrogens, treatment with the Vivelle estradiol transdermal system should be initiated 1 week after withdrawal of oral hormone replacement therapy, or sooner if menopausal symptoms reappear in less than 1 week.

Therapeutic Regimen

Vivelle may be given continuously in patients who do not have an intact uterus. In those patients with an intact uterus, Vivelle may be given on a cyclic schedule (e.g., 3 weeks on drug followed by 1 week off drug).

HOW SUPPLIED

Vivelle estradiol transdermal system 0.0375 mg/day - each 11.0 cm^2 system contains 3.28 mg of estradiol USP for nominal* delivery of 0.0375 mg of estradiol per day.

Patient Calendar Pack of 8 systems ..... NDC 0083-2325-08
Carton of 6 Patient Calendar Packs of 8 systems ..... NDC 0083-2325-62
Carton of 24 systems ..... NDC 0083-2325-25

Vivelle estradiol transdermal system 0.05 mg/day - each 14.5 cm^2 system contains 4.33 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 systems ..... NDC 0083-2326-08
Carton of 6 Patient Calendar Packs of 8 systems ..... NDC 0083-2326-62
Carton of 24 systems ..... NDC 0083-2326-25

Vivelle estradiol transdermal system 0.075 mg/day - each 22.0 cm^2 system contains 6.57 mg of estradiol USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 systems ..... NDC 0083-2327-08
Carton of 6 Patient Calendar Packs of 8 systems ..... NDC 0083-2327-62
Carton of 24 systems ..... NDC 0083-2327-25

Vivelle estradiol transdermal system 0.1 mg/day - each 29.0 cm^2 system contains 8.66 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 systems ..... NDC 0083-2328-08
Carton of 6 Patient Calendar Packs of 8 systems ..... NDC 0083-2328-62
Carton of 24 systems ..... NDC 0083-2328-25

*See DESCRIPTION.

Do not store above 86°F (30°C). Do not store unpouched. Apply immediately upon removal from the protective pouch.

C95-40 (Rev. 9/95)

Information for the Patient

VIVELLE™

estradiol transdermal system

1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE").

If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

INTRODUCTION

Your doctor has prescribed the Vivelle system for the treatment of your menopausal symptoms. During menopause, production of estrogen hormones by your body decreases well below the amounts normally produced during your fertile years. In many women, this decrease in estrogen production causes uncomfortable symptoms, most noticeably hot flushes and sleep disturbance. Estrogens can be given to reduce or eliminate these symptoms.

The Vivelle system that your doctor has prescribed for you releases small amounts of estradiol through the skin in a continuous way. Estradiol is the same hormone that your ovaries produce abundantly before menopause. The dose of estradiol you require will depend upon your individual response. The dose is adjusted by the size of the Vivelle system used; the systems are available in four sizes.

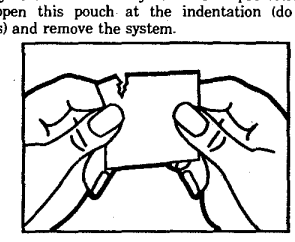
INFORMATION ABOUT VIVELLE

How Vivelle Works

Vivelle contains estradiol. When applied to the skin as directed below, the Vivelle system releases estradiol, which flows through the skin into the bloodstream.

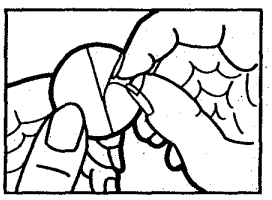
How and Where to Apply Vivelle

Each system is individually sealed in a protective pouch. Tear open this pouch at the indentation (do not use scissors) and remove the system.

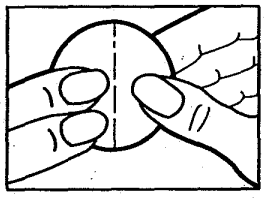


A stiff protective liner covers the adhesive side of the system—the side that will be placed against your skin. This liner must be removed before applying the system. Hold the unit with the protective liner facing you.

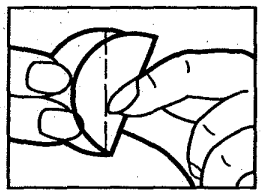
Peel off one side of the protective liner and discard it. Try to avoid touching the sticky side of the system with your fingers.



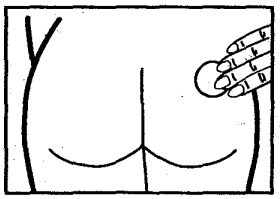
Using the other half of the liner as a handle, apply the sticky side of the system to a dry area of the skin on the trunk of the body (including the buttocks and abdomen). Press the sticky side on the skin and smooth down.



Fold back the remaining side of the system. Grasp the straight edge of the protective liner and pull it off the system.



Press the system firmly in place.



Some women may find that it is more comfortable to wear Vivelle on the buttocks. *Do not apply Vivelle to your breasts.* The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub the system off. Apply the system immediately after opening the pouch and removing the protective liner. Press the system firmly in place with the palm of your hand for about 10 seconds, making sure there is good contact, especially around the edges.

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The Vivelle system should be worn continuously until it is time to replace it with a new system. You may wish to experiment with different locations when applying a new system, to find ones that are most comfortable for you and where clothing will not rub on the system.

When to Apply Vivelle

The Vivelle system should be replaced twice weekly. Your Vivelle package contains a calendar checklist on the back to help you remember a schedule. Mark the 2-day schedule you plan to follow. Always change the system on the 2 days of the week you have marked.

When changing the system, remove the used Vivelle system and discard it. Any adhesive that might remain on your skin can be easily rubbed off. Then place the new Vivelle system on a different skin site. (The same skin site should not be used again for at least 1 week after removal of the system.)

Please note: Contact with water when you are bathing, swimming, or showering will not affect the system. In the unlikely event that a system should fall off, put this same system back on and continue to follow your original treatment schedule. If necessary, you may apply a new system but continue to follow your original schedule.

Benefits of Treatment With Vivelle

Regular use of Vivelle twice weekly offers relief of moderate-to-severe symptoms of menopause.

Small quantities of the naturally occurring hormone estradiol are absorbed through the skin from the Vivelle system, ensuring a continuous supply of circulating hormone in the body.

USES OF ESTROGEN

To reduce moderate-to-severe menopausal symptoms. Estrogens are hormones produced by the ovaries. The decrease in the amount of estrogen that occurs in all women, usually between ages 45 and 55, causes the menopause. Sometimes the ovaries are removed by an operation, causing "surgical menopause." When the amount of estrogen begins to decrease, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest or sudden intense episodes of heat and sweating ("hot flashes"). The use of drugs containing estrogens can help the body adjust to lower estrogen levels.

Some women have only mild menopausal symptoms, or none at all, and do not need estrogen therapy for these particular symptoms. Other women may need estrogens for a few months while their bodies adjust to lower estrogen levels. For the treatment of menopausal symptoms only, most women need estrogen replacement therapy for no longer than 6 months.

To treat vulval and vaginal atrophy (itching, burning, dryness in or around the vagina, difficulty or burning on urination) *associated with menopause.*

To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.

WHEN ESTROGENS SHOULD NOT BE USED

During pregnancy (see Boxed Warning). If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.

If you have unusual vaginal bleeding that has not been evaluated by your doctor (see Boxed Warning). Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.

If you have had cancer. Since estrogens increase the risk of certain types of cancer, you should not use estrogens if you ever have had cancer of the breast or uterus.

If you have any circulation problems. Estrogen therapy should be used only after consultation with your doctor and only in recommended doses. Patients with a tendency for abnormal blood clotting should avoid estrogen use (see DANGERS OF ESTROGENS, below).

When they are ineffective. During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.

After childbirth or when breastfeeding a baby. Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see DANGERS OF ESTROGENS, below).

If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your healthcare provider.

DANGERS OF ESTROGENS

Cancer of the uterus. The risk of developing cancer of the uterus gets higher the longer estrogens are used and when larger doses are taken. One study showed that when estrogens are discontinued, this increased risk of cancer seems to fall off quickly. Three other studies showed that the risk for uterine cancer stayed high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk, *it is important to take the lowest dose that works and to take it only as long as you need it.* Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see OTHER INFORMATION, below).

If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.

Cancer of the breast. The majority of studies have shown no association between the usual doses used for estrogen replacement therapy and breast cancer. Some studies have suggested a possible increased incidence of breast cancer in those women taking estrogens for prolonged periods of time and especially if higher doses are used.

Regular breast examinations by a health professional and monthly self-examination are recommended for women receiving estrogen therapy, as they are for all women.

Gallbladder disease. Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

Abnormal blood clotting. Taking estrogens may increase the risk of blood clots. These clots can cause a stroke, heart attack, or pulmonary embolus, any of which may be fatal. However, most studies of low-dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

- Headache.
- Nausea and vomiting.
- Breast tenderness or enlargement.
- Enlargement of benign tumors ("fibroids") of the uterus.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face. Skin irritation, redness, or rash may occur at the site of application.

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things: *See your doctor regularly.* While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.

Reassess your need for estrogens. You and your doctor should reevaluate whether or not you still need estrogens at least every 6 months.

Be alert for signs of trouble. Report these or any other unusual side effects to your doctor immediately:

- Abnormal bleeding from the vagina.
- Pains in the calves or chest, sudden shortness of breath, or coughing blood (indicating possible clots in the legs, heart, or lungs).
- Severe headache, dizziness, faintness, or changes in vision (indicating possible clots in the brain or eye).
- Breast lumps.
- Yellowing of the skin or eyes.
- Pain, swelling, or tenderness in the abdomen.
- Skin irritation, redness, or rash.

OTHER INFORMATION

If your uterus has not been removed, your doctor may choose to prescribe a progestin, a different hormonal drug to be used in association with estrogen treatment. Progestins lower the risk of developing endometrial hyperplasia, a possible precancerous condition of the uterine lining, which may occur while using estrogen. There are possible additional risks that may be associated with the inclusion of a progestin in estrogen treatment. The possible risks include unfavorable effects on blood fats and sugars, as well as a possible further increase in breast cancer risk that may be associated with long-term estrogen use.

Some research has suggested that estrogen taken *without progestins* may protect women against developing heart disease. However, this effect of estrogen is not certain.

You are cautioned to discuss very carefully with your doctor or healthcare provider all the possible risks and benefits of long-term estrogen and progestin treatment, as they affect you personally.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

Keep this and all drugs out of the reach of children. In case of overdose, remove the system and call your doctor, hospital, or poison control center immediately.

This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling.

C95-34 (Rev. 8/95)
C95-40/C95-34 (Rev. 9/95)

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Ciba-Geigy Corporation
Pharmaceuticals Division
Summit, NJ 07901

Shown in Product Identification Guide, page 310

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DULCOLAX® **OTC**
[*dul'co-lax*]
brand of bisacodyl USP

DESCRIPTION AND CLINICAL PHARMACOLOGY

Dulcolax is a contact stimulant laxative, administered either orally or rectally, which acts directly on the colonic mucosa to produce normal peristalsis throughout the large intestine. The active ingredient in Dulcolax, bisacodyl, is a colorless, tasteless compound that is practically insoluble in water or alkaline solution. Its chemical name is: bis(p-acetoxyphenyl)-2-pyridylmethane. Bisacodyl is very poorly absorbed, if at all, in the small intestine following oral administration, or in the large intestine following rectal administration. On contact

Continued on next page

Ciba Self-Medication, Inc.—Cont.

with the mucosa or submucosal plexi of the large intestine, bisacodyl stimulates sensory nerve endings to produce parasympathetic reflexes resulting in increased peristaltic contractions of the colon. It has also been shown to promote fluid and ion accumulation in the colon, which increases the laxative effect. A bowel movement is usually produced approximately 6 hours after oral administration (8–12 hours if taken at bedtime), and approximately 15 minutes to 1 hour after rectal administration, providing satisfactory cleansing of the bowel which may, under certain circumstances, obviate the need for colonic irrigation.

Dulcolax (brand of bisacodyl USP) is available as enteric coated tablets of 5 mg each or as suppositories of 10 mg each. Each tablet also contains: acacia, acetylated monoglyceride, carnauba wax, cellulose acetate phthalate, corn starch, D&C Red No. 30 aluminum lake, D&C Yellow No. 10 aluminum lake, dibutyl phthalate, docusate sodium, gelatin, glycerin, iron oxides, kaolin, lactose, magnesium stearate, methylparaben, pharmaceutical glaze, polyethylene glycol, povidone, propylparaben, sodium benzoate, sorbitan monooleate, sucrose, talc, titanium dioxide, and white wax. Each suppository also contains hydrogenated vegetable oil. Tablets and suppositories contain less than 0.2 mg sodium per dosage unit and are thus dietetically sodium-free.

INDICATIONS AND USAGE

For the relief of occasional constipation and irregularity. For use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray endoscopic examination. Dulcolax will not replace the colonic irrigations usually given patients before intracolonic surgery, but is useful in the preliminary emptying of the colon prior to those procedures. Dulcolax may also be used in postoperative care (i.e., restoration of normal bowel hygiene), antepartum care, postpartum care, and in preparation for delivery.

CONTRAINDICATIONS

Stimulant laxatives, such as Dulcolax, are contraindicated for patients with acute surgical abdomen, appendicitis, rectal bleeding, gastroenteritis, or intestinal obstruction.

WARNINGS AND PRECAUTIONS

Use of Dulcolax is not recommended when abdominal pain, nausea, or vomiting are present. Long term administration of Dulcolax is not recommended in the treatment of chronic constipation. This product should not be used beyond 7 days unless deemed necessary. Rectal bleeding or failure to have a bowel movement after Dulcolax use may indicate a serious condition. If this occurs, the patient should discontinue use of the product.

This and all medication should be kept out of the reach of children.

Pregnancy Category B

Teratology

Reproduction studies of oral doses of Dulcolax (bisacodyl) have been performed in rats administered up to 70 times the human dose, and have revealed no evidence of impaired fertility or damage to the fetus. At the dose which equated to 70 times the human dose, there was some evidence of lower litter survival at weaning. There are, however, no adequate and well-controlled studies in pregnant women, hence Dulcolax should be used during pregnancy only at the discretion of the physician.

Extent of Drug Absorption

In a pharmacokinetic (crossover) study involving 12 patients (Roth, 1988), plasma levels of bisacodyl were measured following oral administration of a 10 mg reference solution and two 5 mg Dulcolax tablets, and following rectal administration of one 10 mg Dulcolax suppository. With the solution dose, the average Cmax was 237 ng/ml; with the tablet dose, the average Cmax was 26 ng/ml (11% of the solution Cmax); with the suppository dose, in six patients the plasma level was below the limit of detection, and in the remaining six patients, the average Cmax was 31 ng/ml (13% of the solution Cmax in those particular patients). These data demonstrate the low level of systemic absorption of bisacodyl resulting from Dulcolax use.

ADVERSE DRUG REACTIONS

The process of restoring normal bowel function by use of a laxative may result in some abdominal discomfort.

OVERDOSAGE

There are no specific antidotes that are required to be administered in the event of overdosage; however, supportive care may be required in order to prevent dehydration and/or electrolyte imbalance.

DOSAGE AND ADMINISTRATION

Tablets

Adults and children 12 years of age and over: Take 2 or 3 tablets (usually 2) in a single dose once daily.

Children 6 to under 12 years of age: Take 1 tablet once daily.

Expect results in 8–12 hours if taken at bedtime or within 6 hours if taken before breakfast. Do not chew or crush tablets. Do not administer tablets within 1 hour after taking an antacid or milk.

Children under 6 years of age: Oral administration is not recommended due to the requirement to swallow tablets whole.

Suppositories

Adults and children 12 years of age and over: Use 1 suppository once daily. Remove foil wrapper. Lie on your side and, with pointed end first, push suppository high into the rectum so it will not slip out. Retain it for 15 to 20 minutes. If you feel the suppository must come out immediately, it was not inserted high enough and should be pushed higher.

Children under 12 years of age: One half of one 10 mg suppository once daily.

If the suppository seems soft, hold in foil wrapper under cold water for one or two minutes. In the presence of anal fissures or hemorrhoids, suppository may be coated at the tip with petroleum jelly before insertion.

Preparation for x-ray endoscopy: For barium enemas, no food should be given following oral administration to prevent reaccumulation of material in the rectum, and a suppository should be administered one to two hours prior to examination.

HOW SUPPLIED

Dulcolax, brand of bisacodyl, is supplied as either light orange enteric coated tablets of 5 mg each in sample packages of 2 or boxes of 4, 10, 25, 50, 100 (OTC as well as hospital unit doses) and 1000, or as suppositories of 10 mg each in sample packages of 1 or boxes of 4, 8, 16, 50, and 500.

NDC 0067-6200 (tablets)

NDC 0067-6100 (suppositories)

Store Dulcolax tablets and suppositories at temperatures below 77°F (25°C). Avoid excessive humidity.

Dulcolax is also supplied in a Bowel Prep Kit. Each kit contains one Dulcolax suppository (10 mg), four Dulcolax tablets (5 mg each), and complete patient instructions.

BIBLIOGRAPHY

Roth, V.W. et al: "Pharmacokinetics and Laxative Effect of Bisacodyl after Administration of Various Dosage Forms"; Arzneim.-Forsch. *38* (I), No. 4, pp. 570–4 (1988).

Additional literature references available upon request.

Shown in Product Identification Guide, page 308

HABITROL® ℞

(nicotine transdermal system)

Systemic delivery of 21, 14, or 7 mg/day over 24 hours

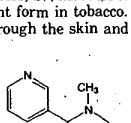
Prescribing Information

DESCRIPTION

Habitrol is a transdermal system that provides systemic delivery of nicotine following its application to intact skin for 24 hours.

Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a colorless-to-pale yellow, freely water-soluble, strongly alkaline, oily, volatile, hygroscopic liquid obtained from the tobacco plant. Nicotine has a characteristic pungent odor and turns brown on exposure to air or light. Of its two stereoisomers, S(-)-nicotine is the more active and is the more prevalent form in tobacco. The free alkaloid is absorbed rapidly through the skin and respiratory tract.

Structural Formula



Chemical Name: S-3(1-methyl-2-pyrrolidinyl) pyridine

Molecular Formula: $C_{10}H_{14}N_2$

Molecular Weight: 162.23

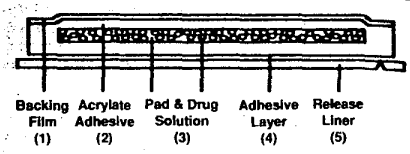
Ionization Constants: $pK_{a1}=7.84$, $pK_{a2}=3.04$

Octanol-Water Partition Coefficient: 15:1 at pH 7

Habitrol systems are round, flat, 0.6-mm-thick multi-layer units containing nicotine as the active agent. Proceeding from the visible surface toward the surface attached to the skin are: (1) a tan-colored aluminized backing film; (2) a pressure-sensitive acrylate adhesive; (3) a layer containing a methacrylic acid copolymer solution of nicotine dispersed in a pad of nonwoven viscose and cotton; (4) an adhesive layer similar in composition to (2) above; (5) a protective aluminized release liner which overlays the adhesive layer and must be removed prior to use.

[See Figure at top of next column.]

Nicotine is the active ingredient; other components of the system are pharmacologically inactive.



The amount of nicotine delivered to the patient from each system (29 mcg/cm²-h) is nearly proportional to the surface area. About 60% of the total amount of nicotine remains in the system 24 hours after application. Habitrol systems are labeled as to the dose actually absorbed by the patient. The dose of nicotine absorbed from a Habitrol system represents 98% of the amount released from the system in 24 hours.

Dose Absorbed in 24 hours (mg/day)	System Surface Area (cm^2)	Total Nicotine Content (mg)
21	30	52.5
14	20	35.0
7	10	17.5

CLINICAL PHARMACOLOGY

Pharmacologic Action

Nicotine, the chief alkaloid in tobacco products, binds stereoselectively to acetylcholine receptors at the autonomic ganglia, in the adrenal medulla, at neuromuscular junctions, and in the brain. Two types of central nervous system effects are believed to be the basis of nicotine's positively reinforcing properties. A stimulating effect, exerted mainly in the cortex via the locus ceruleus, produces increased alertness and cognitive performance. A "reward" effect via the "pleasure system" in the brain is exerted in the limbic system. At low doses the stimulant effects predominate while at high doses the reward effects predominate. Intermittent intravenous administration of nicotine activates neurohormonal pathways, releasing acetylcholine, norepinephrine, dopamine, serotonin, vasopressin, beta-endorphin, growth hormone, and ACTH.

Pharmacodynamics

The cardiovascular effects of nicotine include peripheral vasoconstriction, tachycardia, and elevated blood pressure. Acute and chronic tolerance to nicotine develops from smoking tobacco or ingesting nicotine preparations. Acute tolerance (a reduction in response for a given dose) develops rapidly (less than 1 hour), however, not at the same rate for different physiologic effects (skin temperature, heart rate, subjective effects). Withdrawal symptoms such as cigarette craving can be reduced in some individuals by plasma nicotine levels lower than those from smoking.

Withdrawal from nicotine in addicted individuals is characterized by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbances, impaired concentration, increased appetite, minor somatic complaints (headache, myalgia, constipation, fatigue), and weight gain. Nicotine toxicity is characterized by nausea, abdominal pain, vomiting, diarrhea, diaphoresis, flushing, dizziness, disturbed hearing and vision, confusion, weakness, palpitations, altered respiration, and hypotension.

The cardiovascular effects of Habitrol 14 mg/day systems used continuously for 24 hours were compared with smoking every hour during waking hours, for 10 days. A small increase in blood pressure was detectable on the first day but not after 10 days. Heart rate was increased by 3%–7% and stroke volume decreased by 5%–12% on the 10th day of application. Habitrol treatment had no significant influence on cutaneous blood flow or skin temperature.

Both smoking and nicotine can increase circulating cortisol and catecholamines, and tolerance does not develop to the catecholamine-releasing effects of nicotine. Changes in the response to a concomitantly administered adrenergic agonist or antagonist should be watched for when nicotine intake is altered during Habitrol therapy and/or smoking cessation (see PRECAUTIONS, Drug Interactions).

Pharmacokinetics

The volume of distribution following IV administration of nicotine is approximately 2 to 3 L/kg and the half-life ranges from 1 to 2 hours. The major eliminating organ is the liver, and average plasma clearance is about 1.2 L/min; the kidney and lung also metabolize nicotine. There is no significant skin metabolism of nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound. The primary metabolite of nicotine in plasma, cotinine, has a half-life of 15 to 20 hours and concentrations that exceed nicotine by 10-fold.

Plasma-protein binding of nicotine is <5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have significant consequences.

The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxycotinine (45% of the dose). About 10% of nicotine is excreted unchanged in the urine. As much as 30% may be excreted in the urine with high urine flow rates and urine acidification below pH 5.

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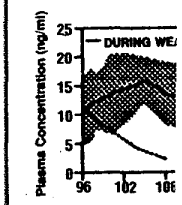

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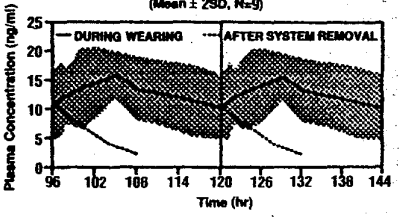
the clinics.

The pharmacokinetic model which best fits the plasma nicotine concentrations from Habitrol systems is an open, two-compartment disposition model with a skin depot through which nicotine enters the central circulation compartment. The nicotine from the drug matrix is released slowly from the system. Therefore, the decline of plasma nicotine concentrations during the last 12 hours is determined primarily by release of nicotine from the system through the skin.

Steady-State Plasma Nicotine Concentrations for Two Consecutive Applications of Habitrol 21 mg/day (Mean ± 2SD, N=9)



Following an initial lag time of 1–2 hours, nicotine concentrations increase to a broad peak between 6 and 12 hours and then decrease gradually. Steady state for nicotine is attained within 2 days of initiating Habitrol treatment and average plasma nicotine concentrations are, on average, 25% higher compared to single dose applications. Upon application of a new system and removal of the old system there is, in some patients, a slight and transient (30–60 min.) increase in nicotine plasma concentration and its variability. Plasma nicotine concentrations are proportional to dose (ie, linear kinetics are observed) for the three dosages of Habitrol systems. Nicotine kinetics are similar for all sites of application on the back, abdomen, or side.

Following removal of Habitrol systems, plasma nicotine concentrations decline in an exponential fashion with an apparent mean half-life of 3–4 hours (see dotted line in graph) compared with 1–2 hours for IV administration, due to continued absorption from the skin depot. Most nonsmoking patients will have nondetectable nicotine concentrations in 10 to 12 hours.

Steady-State Nicotine Pharmacokinetic Parameters for Habitrol Systems
(mean, standard deviation, range)

Parameter	14 mg/day (N=9)			21 mg/day (N=9)		
(units)	Mean	SD	Range	Mean	SD	Range
C_{max} (ng/mL)	12	4	6–16	17	2	13–19
C_{avg} (ng/mL)	9	3	5–12	13	2	9–17
C_{min} (ng/mL)	6	2	3–10	9	2	7–14
T_{max} (hrs)	5	3	0– 8	6	3	2– 9

C_{max}: maximum observed plasma concentration
C_{avg}: average plasma concentration
C_{min}: minimum observed plasma concentration
T_{max}: time of maximum plasma concentration

Clinical Studies

The efficacy of Habitrol treatment as an aid to smoking cessation was demonstrated in three placebo-controlled, double-blind trials in otherwise healthy patients smoking at least one pack per day (N=792). In two of the trials Habitrol therapy was combined with concomitant support and in one trial Habitrol was used without concomitant support. In all three trials, patients were treated for 7 weeks (3 weeks of titration and 4 weeks of maintenance) followed by 3 weeks of weaning. Quitting was defined as total abstinence from smoking as measured by patient diary and verified by expired carbon monoxide. The "quit rates" are the proportions of all persons initially enrolled who abstained after week 3.

The two trials in otherwise healthy smokers with concomitant support showed that Habitrol therapy was more effective than placebo after 7 weeks. Quit rates were still significantly different after the additional 3-week weaning period. The quit rates varied approximately 3-fold among clinics for each treatment when Habitrol therapy was used with a concomitant support program. Data from these two studies (N=516) are combined in the Quit Rate table. Greater variability and decreased quit rates were demonstrated in both placebo and Habitrol treatment groups when concomitant support was not employed (N=276, see table).

[See table on top of page.]

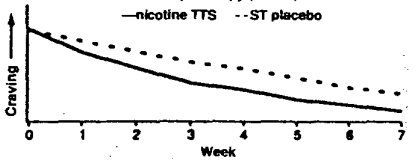
Patients who used Habitrol treatment in clinical trials had a significant reduction in craving for cigarettes, a major nicotine withdrawal symptom, as compared to placebo-treated patients (see graph). Reduction in craving, as with quit rate, is quite variable. This variability is presumed to be due to inherent differences in patient populations, eg, patient motivation, concomitant illnesses, number of cigarettes smoked per day, number of years smoking, exposure to other smokers, socioeconomic status, etc, as well as differences among the clinics.

Quit Rates After Week 3 by Treatment

Concomitant Support	Treatment	Number of Patients	After 7 Weeks (range)	After Weaning (range)
Yes†	Habitrol	260	19–54%	8–43%
	Placebo*	256	9–30%	8–30%
No††	Habitrol	141	4–28%	4–20%
	Placebo*	135	0–24%	0–22%

*Sub Therapeutic (ST) Placebo systems contained 13% of the nicotine found in the respective-sized active system to allow blinding as to color and odor.
†Two trials with 9 clinics, number of patients per treatment ranged from 22 to 39.
††One trial with 5 clinics, number of patients per treatment ranged from 24 to 40.

Severity of Craving by Treatment in the Two Clinical Trials with Concurrent Group Therapy (N=427)



Patients using Habitrol systems dropped out of the trials less frequently than did patients receiving placebo. Quit rates for the 32 patients over age 60 were comparable to the quit rates for the 369 patients aged 60 and under.

Individualization of Dosage

It is important to make sure that patients read the instructions made available to them and have their questions answered. They should clearly understand the directions for applying and disposing of Habitrol systems. They should be instructed to stop smoking completely when the first system is applied.

The success or failure of smoking cessation depends heavily on the quality, intensity, and frequency of supportive care. Patients are more likely to quit smoking if they are seen frequently and participate in formal smoking cessation programs.

The goal of Habitrol therapy is complete abstinence. Significant health benefits have not been demonstrated for reduction of smoking. If a patient is unable to stop smoking by the fourth week of therapy, treatment should probably be discontinued. Patients who have not stopped smoking after 4 weeks of Habitrol therapy are unlikely to quit on that attempt.

Patients who fail to quit on any attempt may benefit from interventions to improve their chances for success on subsequent attempts. Patients who were unsuccessful should be counseled to determine why they failed. Patients should then probably be given a "therapy holiday" before the next attempt. A new quit attempt should be encouraged when the factors that contributed to failure can be eliminated or reduced, and conditions are more favorable.

Based on the clinical trials, a reasonable approach to assisting patients in their attempt to quit smoking is to assign their initial Habitrol dosage using the recommended dosing schedule (see Dosing Schedule). The need for dose adjustment should be assessed during the first 2 weeks. Patients should continue the dose selected with counseling and support over the following month. Those who have successfully stopped smoking during that time should be supported during 4 to 8 weeks of weaning, after which treatment should be terminated.

Therapy should generally begin with the Habitrol 21 mg/day dose (see Dosing Schedule below) except if the patient is small (less than 100 lbs), is a light smoker (less than $^1/_2$ pack of cigarettes per day) or has cardiovascular disease.

Dosing Schedule

	Otherwise Healthy Patients	Other Patients*
Initial/Starting Dose	21 mg/day	14 mg/day
Duration of Treatment	4–8 weeks	4–8 weeks
First Weaning Dose	14 mg/day	7 mg/day
Duration of Treatment	2–4 weeks	2–4 weeks
Second Weaning Dose	7 mg/day	
Duration of Treatment	2–4 weeks	

*small patient (less than 100 lbs)
or light smoker (less than 10 cigarettes/day)
or patient with cardiovascular disease

The symptoms of nicotine withdrawal and excess overlap (see Pharmacodynamics and ADVERSE REACTIONS). Since patients using Habitrol treatment may also smoke intermittently, it may be difficult to determine if patients are experiencing nicotine withdrawal or nicotine excess.

The controlled clinical trials using Habitrol therapy suggest that abnormal dreams are more often symptoms of nicotine excess while flatulence, anxiety, and depression are more often symptoms of nicotine withdrawal.

INDICATIONS AND USAGE

Habitrol treatment is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. Habitrol treatment should be used as a part of a comprehensive behavioral smoking cessation program.

The use of Habitrol systems for longer than 3 months has not been studied.

CONTRAINDICATIONS

Use of Habitrol systems is contraindicated in patients with hypersensitivity or allergy to nicotine or to any of the components of the therapeutic system.

WARNINGS

Nicotine from any source can be toxic and addictive. Smoking causes lung cancer, heart disease, emphysema, and may adversely affect the fetus and the pregnant woman. For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking cessation program should be weighed against the hazard of continued smoking while using Habitrol systems, and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy Warning

Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. Nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that Habitrol treatment can cause fetal harm when administered to a pregnant woman. The effect of nicotine delivery by Habitrol systems has not been examined in pregnancy (see PRECAUTIONS, Other Effects). Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches. If Habitrol therapy is used during pregnancy, or if the patient becomes pregnant while using Habitrol treatment, the patient should be apprised of the potential hazard to the fetus.

Safety Note Concerning Children

The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if Habitrol systems are applied or ingested by children or pets. Used 21 mg/day systems contain about 60% (32 mg) of their initial drug content. Therefore, patients should be cautioned to keep both used and unused Habitrol systems out of the reach of children and pets.

PRECAUTIONS

General

The patient should be urged to stop smoking completely when initiating Habitrol therapy (see DOSAGE AND ADMINISTRATION). Patients should be informed that if they continue to smoke while using Habitrol systems, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the Habitrol dose should be reduced or Habitrol treatment discontinued (see WARNINGS). Physicians should anticipate that concomitant medications may need dosage adjustment (see Drug Interactions).

The use of Habitrol systems beyond 3 months by patients who stop smoking should be discouraged because the chronic consumption of nicotine by any route can be harmful and addicting.

Allergic Reactions: In a 12-week, open-label dermal irritation and sensitization study of Habitrol systems, 22 of 223 patients exhibited definite erythema at 24 hours after application. Upon rechallenge, 3 patients exhibited mild-to-moderate contact allergy. Patients with contact sensitization should be cautioned that a serious reaction could occur from exposure to other nicotine-containing products or smoking.

In the efficacy trials, erythema following system removal was typically seen in about 17% of patients, some edema in 4%, and dropouts due to skin reactions occurred in 6% of patients.

Patients should be instructed to promptly discontinue the Habitrol treatment and contact their physicians if they experience severe or persistent local skin reactions at the site of

Continued on next page

Ciba Self-Medication, Inc.—Cont.

application (eg, severe erythema, pruritus, or edema) or a generalized skin reaction (eg, urticaria, hives, or generalized rash).

Skin Disease: Habitrol systems are usually well tolerated by patients with normal skin, but may be irritating for patients with some skin disorders (atopic or eczematous dermatitis).

Cardiovascular or Peripheral Vascular Diseases: The risks of nicotine replacement in patients with certain cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina) should be carefully screened and evaluated before nicotine replacement is prescribed.

Tachycardia occurring in association with the use of Habitrol treatment was reported occasionally. If serious cardiovascular symptoms occur with Habitrol treatment, it should be discontinued.

Habitrol treatment should generally not be used in patients during the immediate post-myocardial infarction period, patients with serious arrhythmias, and patients with severe or worsening angina pectoris.

Renal or Hepatic Insufficiency: The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or hepatic impairment. However, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Endocrine Diseases: Habitrol treatment should be used with caution in patients with hyperthyroidism, pheochromocytoma, or insulin-dependent diabetes since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease: Nicotine delays healing in peptic ulcer disease; therefore, Habitrol treatment should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Accelerated Hypertension: Nicotine constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, Habitrol treatment should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Information for Patients: A patient instruction sheet is included in the package of Habitrol systems dispensed to the patient. It contains important information and instructions on how to use and dispose of Habitrol systems properly. Patients should be encouraged to ask questions of the physician and pharmacist.

Patients must be advised to keep both used and unused systems out of the reach of children and pets.

Drug Interactions

Smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications.

[See table below.]

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidence of tumors in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumor-initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

Nicotine and cotinine were not mutagenic in the Ames *Salmonella* test. Nicotine induced repairable DNA damage in an *E. coli* test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Pregnancy Category D (see WARNINGS)

The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, an increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of Habitrol treatment on fetal development are unknown. Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

Habitrol treatment should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of use of nicotine replacement by the patient, who may continue to smoke.

Teratogenicity

Animal Studies: Nicotine was shown to produce skeletal abnormalities in the offspring of mice when given doses toxic to the dams (25 mg/kg/day IP or SC).

Human Studies: Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

Other Effects

Animal Studies: A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension (fetal and maternal concentrations were about 20 times those achieved after smoking 1 cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking 1 cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 mg/kg/min nicotine for 20 minutes to pregnant rhesus monkeys (equivalent to smoking about six cigarettes every minute for 20 minutes).

Human Experience: Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low-birth-weight infants and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effects of cigarette smoking on fetal cardiovascular parameters have been studied near term. Cigarettes increased fetal aortic blood flow and heart rate and decreased uterine blood flow and fetal breathing movements. Habitrol treatment has not been studied in pregnant humans.

Labor and Delivery

Habitrol systems are not recommended to be left on during labor and delivery. The effects of nicotine on the mother or the fetus during labor are unknown.

Nursing Mothers

Caution should be exercised when Habitrol therapy is administered to nursing women. The safety of Habitrol treatment in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk-to-plasma ratio averages 2.9. Nicotine is absorbed orally. An infant has the ability to clear nicotine by hepatic first-pass clearance; however, the efficiency of removal is probably lowest at birth. The nicotine concentrations in milk can be expected to be lower with Habitrol treatment when used as directed than with cigarette smoking, as maternal plasma nicotine concentrations are generally reduced with nicotine replacement. The risk of exposure of the infant to nicotine from Habitrol systems should be weighed against the risks associated with the infant's exposure to nicotine from continued smoking by the mother (passive smoke exposure and contamination of breast milk with other components of tobacco smoke) and from Habitrol systems alone or in combination with continued smoking.

Pediatric Use

Habitrol systems are not recommended for use in children because the safety and effectiveness of Habitrol treatment in children and adolescents who smoke have not been evaluated.

Geriatric Use

Forty-eight patients over the age of 60 participated in clinical trials of Habitrol therapy. Habitrol therapy appeared to be as effective in this age group as in younger smokers.

May Require a Decrease in Dose at Cessation of Smoking	Possible Mechanism
Acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, theophylline	Deinduction of hepatic enzymes on smoking cessation
Insulin	Increase of subcutaneous insulin absorption with smoking cessation
Adrenergic antagonists (eg, prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation
May Require an Increase in Dose at Cessation of Smoking	**Possible Mechanism**
Adrenergic agonists (eg, isoproterenol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation

ADVERSE REACTIONS

Assessment of adverse events in the 792 patients who participated in controlled clinical trials is complicated by the occurrence of GI and CNS effects of nicotine withdrawal as well as nicotine excess. The actual incidences of both are confounded by concurrent smoking by many of the patients. In the trials, when reporting adverse events, the investigators did not attempt to identify the cause of the symptom.

Topical Adverse Events

The most common adverse event associated with topical nicotine is a short-lived erythema, pruritus, or burning at the application site, which was seen at least once in 35% of patients on Habitrol treatment in the clinical trials. Local erythema after system removal was noted at least once in 17% of patients and local edema in 4%. Erythema generally resolved within 24 hours. Cutaneous hypersensitivity (contact sensitization) occurred in 2% of patients on Habitrol treatment (see PRECAUTIONS, Allergic Reactions).

Probably Causally Related

The following adverse events were reported more frequently in Habitrol-treated patients than in placebo-treated patients or exhibited a dose response in clinical trials.

Digestive system—Diarrhea*, dyspepsia*.
Mouth/Tooth disorders—Dry mouth.
Musculoskeletal system—Arthralgia*, myalgia*.
Nervous system—Abnormal dreams†, somnolence†.

Frequencies for 21 mg/day system
* Reported in 3% to 9% of patients.
† Reported in 1% to 3% of patients.
Unmarked if reported in <1% of patients.

Causal Relationship Unknown

Adverse events reported in Habitrol- and placebo-treated patients at about the same frequency in clinical trials are listed below. The clinical significance of the association between Habitrol treatment and these events is unknown, but they are reported as alerting information for the clinician.

Body as a whole—Allergy†, back pain†.
Cardiovascular system—Hypertension*.
Digestive system—Abdominal pain†, constipation†, nausea*, vomiting.
Nervous system—Dizziness*, concentration impaired†, headache (17%), insomnia*.
Respiratory system—Cough increased†, pharyngitis†, sinusitis†.
Urogenital system—Dysmenorrhea*.

Frequencies for 21 mg/day system
* Reported in 3% to 9% of patients.
† Reported in 1% to 3% of patients.
Unmarked if reported in <1% of patients.

DRUG ABUSE AND DEPENDENCE

Habitrol systems are likely to have a low abuse potential based on differences between it and cigarettes in four characteristics commonly considered important in contributing to abuse: much slower absorption, much smaller fluctuations in blood levels, lower blood levels of nicotine, and less frequent use (ie, once daily).

Dependence on nicotine polacrilex chewing gum replacement therapy has been reported. Such dependence might also occur from transference to Habitrol systems of tobacco-based nicotine dependence. The use of the system beyond 3 months has not been evaluated and should be discouraged. To minimize the risk of dependence, patients should be encouraged to withdraw gradually from Habitrol treatment after 4 to 8 weeks of usage. Recommended dose reduction is to progressively decrease the dose every 2 to 4 weeks (see DOSAGE AND ADMINISTRATION).

OVERDOSAGE

The effects of applying several Habitrol systems simultaneously or of swallowing Habitrol systems are unknown (see WARNINGS, Safety Note Concerning Children).

The oral LD_{50} for nicotine in rodents varies with species but is in excess of 24 mg/kg; death is due to respiratory paralysis. The oral minimum lethal dose of nicotine in dogs is greater than 5 mg/kg. The oral minimum acute lethal dose for nicotine in human adults is reported to be 40 to 60 mg (< 1 mg/kg).

Two or three Habitrol 30 cm^2 systems in capsules fed to dogs weighing 8–17 kg were emetic, but did not produce any other significant clinical signs. The administration of these patches corresponds to about 6–17 mg/kg of nicotine.

Signs and symptoms of an overdose of Habitrol systems would be expected to be the same as those of acute nicotine poisoning including: pallor, cold sweat, nausea, salivation, vomiting, abdominal pain, diarrhea, headache, dizziness, disturbed hearing and vision, tremor, mental confusion, and weakness. Prostration, hypotension, and respiratory failure may ensue with large overdoses. Lethal doses produce convulsions quickly and death follows as a result of peripheral or central respiratory paralysis or, less frequently, cardiac failure.

Overdose From Topical Exposure

The Habitrol system should be removed immediately if the patient shows signs of overdosage and the patient should seek immediate medical care. The skin surface may be flushed with water and dried. No soap should be used since it may increase nicotine absorption. Nicotine will continue to be delivered into the bloodstream for several hours (see CLINICAL PHARMACOLOGY, Pharmacokinetics) after removal of the system because of a depot of nicotine in the skin.

Overdose From Ingestion

Persons ingesting Habitrol systems should be referred to a health care facility for management. Due to the possibility of nicotine-induced seizures, activated charcoal should be administered. In unconscious patients with a secure airway, instill activated charcoal via nasogastric tube. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the system. Repeated doses of activated charcoal should be administered as long as the system remains in the gastrointestinal tract since it will continue to release nicotine for many hours.

Management of Nicotine Poisoning

Other supportive measures include diazepam or barbiturates for seizures, atropine for excessive bronchial secretions or diarrhea, respiratory support for respiratory failure, and vigorous fluid support for hypotension and cardiovascular collapse.

DOSAGE AND ADMINISTRATION

Patients must desire to stop smoking and should be instructed to *stop smoking immediately* as they begin using Habitrol therapy. The patient should read the patient instruction sheet on Habitrol treatment and be encouraged to ask any questions. Treatment should be initiated with Habitrol 21 mg/day or 14 mg/day systems (see CLINICAL PHARMACOLOGY, Individualization of Dosage). Dosage cannot be adjusted by cutting a Habitrol system.

Once the appropriate dosage is selected the patient should begin 4–6 weeks of therapy at that dosage. The patient should stop smoking cigarettes completely during this period. If the patient is unable to stop cigarette smoking within 4 weeks, Habitrol therapy should probably be stopped, since few additional patients in clinical trials were able to quit after this time.

Recommended Dosing Schedule for Healthy Patients[a]
(see Individualization of Dosage)

Dose	Duration
Habitrol 21 mg/day	First 6 Weeks
Habitrol 14 mg/day	Next 2 Weeks[b]
Habitrol 7 mg/day	Last 2 Weeks[c]

[a] Start with Habitrol 14 mg/day for 6 weeks for patients who:
—have cardiovascular disease
—weigh less than 100 pounds
—smoke less than $^1/_2$ a pack of cigarettes/day
Decrease dose to Habitrol 7 mg/day for the final 2–4 weeks.

[b] Patients who have successfully abstained from smoking should have their dose of Habitrol reduced after each 2–4 weeks of treatment until the 7 mg/day dose has been used for 2–4 weeks (see Individualization of Dosage).

[c] The entire course of nicotine substitution and gradual withdrawal should take 8–12 weeks, depending on the size of the initial dose. The use of Habitrol beyond 3 months has not been studied.

The Habitrol system should be applied promptly upon its removal from the protective pouch to prevent evaporative loss of nicotine from the system. Habitrol systems should be used only when the pouch is intact to assure that the product has not been tampered with.

Habitrol systems should be applied only once a day to a non-hairy, clean, and dry skin site on the trunk or upper, outer arm. After 24 hours, the used Habitrol system should be removed and a new system applied to an alternate skin site. Skin sites should not be reused for at least a week. Patients should be cautioned not to continue to use the same system for more than 24 hours.

Safety and Handling

Habitrol systems can be a dermal irritant and can cause contact sensitization. Although exposure of health care workers to nicotine from Habitrol systems should be minimal, care should be taken to avoid unnecessary contact with active systems. If active systems are handled, wash with water alone, since soap may increase nicotine absorption. Do not touch eyes. KEEP OUT OF THE REACH OF CHILDREN.

Disposal

When the used system is removed from the skin, it should be folded over and placed in the protective pouch which contained the new system. The used system should be immediately disposed of in such a way to prevent its access by children or pets. See patient information for further directions for handling and disposal.

HOW SUPPLIED

Nicotine Delivery Rate *(in vivo)*	Nicotine in System	System Size	Package Size	NDC Number
21 mg/day	52.5 mg	30 cm^2	30 systems	0067-0810-21
14 mg/day	35.0 mg	20 cm^2	30 systems	0067-0820-14
7 mg/day	17.5 mg	10 cm^2	30 systems	0067-0830-07

Habitrol systems are individually packaged in child-resistant pouches and should not be used if individual pouches are unsealed.

[See table above.]

How to Store

Do not store above 86°F (30°C) because Habitrol systems are sensitive to heat. A slight discoloration of the system is not significant.

Do not store unpouched. Once removed from the protective pouch, Habitrol systems should be applied promptly since nicotine is volatile and the system may lose strength.

The use of this product is covered by U.S. Patent No. 4,597,961.

CAUTION: Federal law prohibits dispensing without prescription.

(Rev. 2/96)

Ciba Self-Medication, Inc.
Dist. by:
Ciba Self-Medication, Inc.
Woodbridge, NJ 07095

HABITROL®

(nicotine transdermal system)
Patient Instructions

IMPORTANT

YOUR DOCTOR HAS PRESCRIBED THIS DRUG FOR YOUR USE ONLY. DO NOT LET ANYONE ELSE USE IT. KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN AND PETS. Nicotine can be very toxic and harmful. Small amounts of nicotine can cause serious illness in children. Even used Habitrol patches contain enough nicotine to poison children and pets. Be sure to throw Habitrol patches away out of the reach of children and pets. If a child puts on Habitrol patches or plays with a Habitrol patch that is out of the sealed pouch, take it away from the child and contact a poison control center, or contact a doctor immediately.

Women: Nicotine in any form may cause harm to your unborn baby if you use nicotine while you are pregnant. Do not use Habitrol patches if you are pregnant or nursing unless advised by your doctor. If you become pregnant while using Habitrol patches or if you think you might be pregnant, stop smoking and don't use Habitrol patches until you have talked to your doctor.

This leaflet will provide you with general information about nicotine and specific instructions about how to use Habitrol patches. It is important that you read it carefully and completely before you start using Habitrol patches. Be sure to read the PRECAUTIONS section before using Habitrol patches, because, as with all drugs, Habitrol treatment has side effects. Since this leaflet is only a summary of information, be sure to ask your doctor if you have any questions or want to know more.

INTRODUCTION

IT IS IMPORTANT THAT YOU ARE FIRMLY COMMITTED TO GIVING UP SMOKING.

Habitrol is a skin patch containing nicotine designed to help you quit smoking cigarettes. When you wear a Habitrol patch, it releases nicotine through the skin into your bloodstream while you're wearing it. The nicotine which is in your skin will still be entering your bloodstream for several hours after you take the patch off.

It is the nicotine in cigarettes that causes addiction to smoking. Habitrol therapy replaces some of the nicotine you crave when you are stopping smoking. Habitrol patches may also help relieve other symptoms of nicotine withdrawal that may occur when you stop smoking such as irritability, frustration, anger, anxiety, difficulty in concentration, and restlessness.

There are three doses of Habitrol. Your doctor has chosen the Habitrol patch with the correct dose for you and may adjust it during the first week or two. After about 6 weeks, your doctor will give you smaller Habitrol patches approximately every two weeks. The smaller patches give you less nicotine. In time, you will be completely off nicotine. You cannot adjust the nicotine dose by cutting a Habitrol patch.

INFORMATION ABOUT HABITROL PATCHES

How Habitrol Patches Work

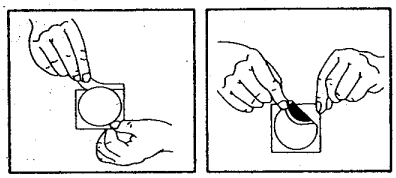
Habitrol patches contain nicotine. When you put a Habitrol patch on your skin, nicotine passes from the patch through the skin and into your blood.

How to Apply a Habitrol Patch

Step 1. Choose a non-hairy, clean, dry area on your trunk or upper, outer part of your arm. Do not put a Habitrol patch on skin that is very oily, burned, broken out, cut, or irritated in any way.

Step 2. Do not remove the Habitrol patch from its sealed, child-resistant, protective pouch until you are ready to use it. Carefully cut open the child-resistant pouch. Discard the used patch you take off by folding it in half and putting it into the opened pouch. Throw it away in the trash out of the reach of children and pets (see Step 7).

Step 3. A shiny protective liner covers the sticky side of the Habitrol patch—the side that will be put on your skin. The liner has a precut slit to help you remove it from the patch. With the silver side facing you, pull the liner away from the Habitrol patch starting at the precut slit. Hold the Habitrol patch at the edge (touch the sticky side as little as possible) and pull off the other piece of the protective liner. Throw away this liner.



Step 4. Immediately apply the sticky side of the Habitrol patch to your skin. Press the Habitrol patch firmly on your skin with the palm of your hand for about 10 seconds. Make sure it sticks well to your skin, expecially around the edges.

Step 5. Wash your hands when you have finished applying the Habitrol patch. Nicotine on your hands could get into your eyes and nose and could cause stinging, redness, or more serious problems.

Step 6. After approximately 24 hours, remove the patch you have been wearing. Choose a *different* place on your skin to apply the next Habitrol patch and repeat Steps 1 to 5. Do not return to a previously used skin site for at least one week. Do not leave the Habitrol patch on for more than 24 hours because it may irritate your skin and because it loses strength after 24 hours.

Step 7. Fold the used Habitrol patch in half with the sticky side together. After you have put on a new Habitrol patch, take its pouch and place the used, folded Habitrol patch inside of it. Throw the pouch in the trash away from children and pets.

When to Apply a Habitrol Patch

If you apply the Habitrol patch at about the same time each day, it will help you to remember when to put on a new Habitrol patch. If you want to change the time when you put on your patch, you can do so. Just remove the Habitrol patch you are wearing and put on a new one. After that, apply the Habitrol patch at the new time each day.

If Your Habitrol Patch Gets Wet

Water will not harm the Habitrol patch you are wearing. You can bathe, swim, use a hot tub, or shower while you are wearing a Habitrol patch.

If Your Habitrol Patch Comes Off

If your Habitrol patch falls off, put on a new one. Remove the Habitrol patch at your regular time to keep your schedule the same, or 24 hours after applying the replacement patch if you wish to change the time each day that you apply a new patch. Before putting on a new patch, make sure you select a non-hairy area which is not irritated and is clean and dry.

Continued on next page

Ciba Self-Medication, Inc.—Cont.

Disposing of a Habitrol Patch
Fold the used Habitrol patch in half with the sticky side together. After you put on a new Habitrol patch, take its opened pouch or aluminum foil and place the used, folded Habitrol patch inside of it. THROW THE POUCH IN THE TRASH AWAY FROM CHILDREN AND PETS.

Storage Instructions
Keep the Habitrol patch in its protective pouch until you are ready to use it. Do not store your Habitrol patches above 86°F (30°C) because the patch is sensitive to heat. Remember, the inside of your car can reach temperatures much higher than this in the summer.

PRECAUTIONS

What to Ask Your Doctor
Ask your doctor about possible problems with Habitrol therapy. Be sure to tell your doctor if you have had any of the following:

- a recent heart attack (myocardial infarction)
- irregular heart beat (arrhythmia)
- severe or worsening heart pain (angina pectoris)
- allergies to drugs
- rashes from adhesive tape or bandages
- skin diseases
- very high blood pressure
- stomach ulcers
- overactive thyroid
- diabetes requiring insulin
- kidney or liver disease

If You Are Taking Medicines
Habitrol patch use, together with stopping smoking, may change the effect of other medicines. It is important to tell your doctor about all the medicines you are taking.

What to Watch For (Adverse Effects)
You should not smoke while using the Habitrol patch. It is possible to get too much nicotine (an overdose), especially if you use a Habitrol patch and smoke at the same time. Signs of an overdose would include bad headaches, dizziness, upset stomach, drooling, vomiting, diarrhea, cold sweat, blurred vision, difficulty with hearing, mental confusion, and weakness. An overdose might cause you to faint.

If Your Skin Reacts to the Habitrol Patch
When you first put on a Habitrol patch, mild itching, burning, or tingling is normal and should go away within an hour. After you remove a Habitrol patch, the skin under the patch might be somewhat red. Your skin should not stay red for more than a day. If you get a skin rash after using a Habitrol patch, or if the skin under the patch becomes swollen or very red, call your doctor. Do not put on a new patch. You may be allergic to one of the components of the Habitrol patch.
If you do become allergic to the nicotine in the Habitrol patch, you could get sick from using cigarettes or other nicotine-containing products.

What to Do When Problems Occur
IF YOU NOTICE ANY WORRISOME SYMPTOMS OR PROBLEMS, TAKE OFF THE HABITROL PATCH AND CALL YOUR DOCTOR AT ONCE.
CHILD-RESISTANT POUCH. DO NOT USE IF INDIVIDUAL POUCHES ARE UNSEALED.

(Rev. 2/96)

Dist. by:
Ciba Self-Medication, Inc.
Woodbridge, NJ 07095

Shown in Product Identification Guide, page 308

EXTRA STRENGTH MAALOX® ANTACID/ANTI-GAS

OTC

Alumina, Magnesia and Simethicone Oral Suspensions and Tablets, Antacid/Anti-Gas

Suspensions and Tablets
☐ **Refreshing Lemon**
Smooth Cherry
Cooling Mint
☐ **Physician-proven Maalox® formula for antacid effectiveness.**
☐ **Simethicone, at a recognized clinical dose, for antiflatulent action.**

DESCRIPTION

Extra Strength Maalox® Antacid/Anti-Gas, a balanced combination of magnesium and aluminum hydroxides plus simethicone, is a non-constipating antacid/anti-gas product to provide symptomatic relief of acid indigestion, heartburn, and gas and upset stomach associated with these symptoms. Available in suspensions in Refreshing Lemon, Smooth Cherry, and Cooling Mint flavors and in tablets in Cooling Mint and assorted (Refreshing Lemon/Smooth Cherry/Cooling Mint) flavors.

COMPOSITION

To provide symptomatic relief of hyperacidity plus alleviation of gas symptoms, each teaspoonful/tablet contains:

Active Ingredients	Extra Strength Maalox® Antacid/Anti-Gas Per Tsp. (5 mL)	Per Tablet
Magnesium Hydroxide	450 mg	350 mg
Aluminum Hydroxide (equivalent to dried gel, USP)	500 mg	350 mg
Simethicone	40 mg	30 mg

INACTIVE INGREDIENTS

Suspensions: Calcium Saccharin, FD&C Red No. 40 (Smooth Cherry only), Flavors, Methylparaben, Propylparaben, Purified Water, Sorbitol and other ingredients.
Tablets: D&C Red No. 30, D&C Yellow No. 10, Dextrose, FD&C Blue No. 1, Flavors, Magnesium Stearate, Mannitol, Saccharin Sodium, Sorbitol, Starch, Sugar.

DIRECTIONS FOR USE

Suspensions; 2 to 4 teaspoonfuls, 4 times per day, or as directed by a physician. Tablets; chew 1 to 3 tablets, 4 times per day, or as directed by a physician.

PATIENT WARNINGS

Do not take more than 12 teaspoonfuls or 12 tablets in a 24-hour period or use the maximum dosage for more than 2 weeks or use if you have kidney disease except under the advice and supervision of a physician. Keep this and all drugs out of the reach of children.

DRUG INTERACTION PRECAUTION

Antacids may interact with certain prescription drugs. If you are presently taking a prescription drug, do not take this product without checking with your physician or other health professional.
To aid in establishing proper dosage schedules, the following information is provided:

	Minimum Recommended Dosage: Extra Strength Maalox® Antacid/Anti-Gas Per 2 Tsp. (10 mL)	Per Tablet
Acid neutralizing capacity	52.2 mEq	NLT 16.7 mEq
Sodium content*	<2 mg	<1.4 mg

*Dietetically insignificant.

Professional Labeling

INDICATIONS

As an antacid for symptomatic relief of hyperacidity associated with the diagnosis of peptic ulcer, gastritis, peptic esophagitis, gastric hyperacidity, heartburn, or hiatal hernia. As an antiflatulent to alleviate the symptoms of gas, including postoperative gas pain.

ADVANTAGES

Among antacids, Extra Strength Maalox® Antacid/Anti-Gas Suspension and Extra Strength Maalox® Antacid/Anti-Gas Tablets are uniquely palatable—an important feature which encourages patients to follow your dosage directions. Extra Strength Maalox® Antacid/Anti-Gas Suspension and Extra Strength Maalox® Antacid/Anti-Gas Tablets have the time-proven, nonconstipating, sodium-free* Maalox® formula—useful for those patients suffering from the problems associated with hyperacidity. Additionally, Extra Strength Maalox® Antacid/Anti-Gas Suspension and Extra Strength Maalox® Antacid/Anti-Gas Tablets contain simethicone to alleviate discomfort associated with entrapped gas.
*Dietetically insignificant.

WARNINGS

Prolonged use of aluminum-containing antacids in patients with renal failure may result in or worsen dialysis osteomalacia. Elevated tissue aluminum levels contribute to the development of the dialysis encephalopathy and osteomalacia syndromes. Small amounts of aluminum are absorbed from the gastrointestinal tract and renal excretion of aluminum is impaired in renal failure. Aluminum is not well removed by dialysis because it is bound to albumin and transferrin, which do not cross dialysis membranes. As a result, aluminum is deposited in bone, and dialysis osteomalacia may develop when large amounts of aluminum are ingested orally by patients with impaired renal function.
Aluminum forms insoluble complexes with phosphate in the gastrointestinal tract, thus decreasing phosphate absorption. Prolonged use of aluminum-containing antacids by normophosphatemic patients may result in hypophosphatemia if phosphate intake is not adequate. In its more severe forms, hypophosphatemia can lead to anorexia, malaise, muscle weakness, and osteomalacia.

HOW SUPPLIED

Extra Strength Maalox® Antacid/Anti-Gas Suspensions
Available in Refreshing Lemon in the following sizes: 5 fl. oz. (148 mL) (0067-0333-62), 12 fl. oz. (355 mL) (0067-0333-71) and 26 fl. oz. (769 mL) (0067-0333-44).
Smooth Cherry is available in plastic bottles of 12 fl. oz. (355 mL) (0067-0336-71) and 26 fl. oz. (769 mL) (0067-0336-44).
Cooling Mint is available in plastic bottles of 12 fl. oz. (355 mL) (0067-0338-71) and 26 fl. oz. (769 mL) (0067-0338-44).
Extra Strength Maalox® Antacid/Anti-Gas Cooling Mint Tablets are available in bottles of 38 tablets (0067-0345-38) and 75 tablets (0067-0345-75).
Extra Strength Maalox® Antacid/Anti-Gas assorted flavors tablets are available in bottles of 38 tablets (0067-7214-38) and 75 tablets (0067-7214-75).

MAALOX®

OTC

Magnesia and Alumina Oral Suspension Antacid

Liquids
Mint Flavored
Cherry Creme

DESCRIPTION

Maalox® Antacid is used for the relief of acid indigestion, heartburn, sour stomach and upset stomach associated with these symptoms.

Active Ingredients	Maalox Suspension 5 mL teaspoon
Magnesium Hydroxide	200 mg
Aluminum Hydroxide (equivalent to dried gel, USP)	225 mg

INACTIVE INGREDIENTS

Calcium saccharin, flavors, methylparaben, propylparaben, sorbitol, purified water and other ingredients.

	Minimum Recommended Dosage: Maalox Suspension Per 2 Tsp. (10 mL)
Acid neutralizing capacity	NLT 26.6 mEq
Sodium content	NMT 3 mg

DIRECTIONS FOR USE

Two to four teaspoonfuls, four times a day or as directed by a physician.

PATIENT WARNINGS

Do not take more than 16 teaspoonfuls in a 24-hour period or use the maximum dosage for more than 2 weeks or use if you have kidney disease except under the advice and supervision of a physician. Keep this and all drugs out of the reach of children.

DRUG INTERACTION PRECAUTION

Antacids may interact with certain prescription drugs. If you are presently taking a prescription drug, do not take this product without checking with your physician or other health professional.

Professional Labeling

INDICATIONS

As an antacid for symptomatic relief of hyperacidity associated with the diagnosis of peptic ulcer, gastritis, peptic

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Ciba Self-Medication, Inc.—Cont.

delivery system of SLOW FE is designed to maximize the release of ferrous sulfate in the duodenum and the jejunum where it is best tolerated and absorbed. SLOW FE has been clinically shown to be associated with a lower incidence of constipation, diarrhea and abdominal discomfort when compared to an immediate release iron tablet[1] and a leading sustained release iron capsule.[2]

FORMULA

Each tablet contains: Active Ingredient: 160 mg dried ferrous sulfate USP, equivalent to 50 mg elemental iron. Inactive Ingredients: cetostearyl alcohol, hydroxypropyl methylcellulose, lactose, magnesium stearate, polysorbate 80, talc, titanium dioxide, yellow iron oxide, FD&C blue #2 aluminum lake.

DOSAGE

ADULTS—one or two tablets daily or as recommended by a physician. A maximum of four tablets daily may be taken. CHILDREN—one tablet daily. Tablets must be swallowed whole.

WARNING

The treatment of any anemic condition should be under the advice and supervision of a physician. As oral iron products interfere with absorption of oral tetracycline antibiotics; these products should not be taken within two hours of each other. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

Keep this and all drugs out of the reach of children. Close bottles tightly. Contains iron, which can be harmful or fatal to children in large doses. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

Tamper-Evident Packaging.

HOW SUPPLIED

Blister Packages of 30 and 60, and bottles of 100 supplied in Child-Resistant packaging.

Do not store above 30°C (86°F). Protect from moisture.

REFERENCES

1. Brock C et al. Adverse effects of iron supplementation: A comparative trial of a wax-matrix iron preparation and conventional ferrous sulfate tablets. *Clin Ther.* 1985; 7:I–VI.
2. Brock C, Curry H. Comparative incidence of side effects of a wax-matrix and a sustained-release iron preparation. *Clin Ther.* 1985;7:492–496.

Shown in Product Identification Guide, page 308

SLOW FE® WITH FOLIC ACID OTC

(Slow Release Iron – Folic Acid)

DESCRIPTION

Slow Fe + Folic Acid delivers 50 mg. elemental iron (160 mg. dried ferrous sulfate) using the unique wax matrix delivery system described above (for SLOW FE® Slow Release Iron Tablets) plus 400 mcg. folic acid.

Provides women of childbearing potential with the daily target level of folic acid to reduce the risk of neural tube birth defects. These birth defects are rare, but serious, and occur within 28 days of conception, often before a woman knows she's pregnant.

FORMULA

Each tablet contains: Active Ingredients: 160 mg. dried ferrous sulfate, USP (equivalent to 50 mg. elemental iron) and 400 mcg. folic acid. Inactive Ingredients: cetostearyl alcohol, hydroxypropyl methylcellulose, lactose, magnesium stearate, polysorbate 80, talc, titanium dioxide, yellow iron oxide.

DOSAGE

ADULTS—One or two tablets once a day or as recommended by a physician. A maximum of two tablets daily may be taken. CHILDREN UNDER 12—Consult a physician. Tablets must be swallowed whole.

WARNING

The treatment of any anemic condition should be under the advice and supervision of a physician. As oral iron products interfere with absorption of oral tetracycline antibiotics, these products should not be taken within two hours of each other. Intake of folic acid from all sources should be limited to 1000 mcg. per day to prevent the masking of Vitamin B_{12} deficiencies. Should you become pregnant while using this product, consult a physician as soon as possible about good prenatal care and the continued use of this product. If you are already pregnant or nursing a baby, seek the advice of a health care professional before using this product. KEEP THIS PRODUCT AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN: Contains iron, which can be harmful or fatal to children in large doses. In case of accidental overdose, contact a physician or a poison control center immediately.

HOW SUPPLIED

Blister packages of 20 supplied in Child-Resistant packaging. Do not store above 30°C (86°F). Protect from moisture.

CHILD-RESISTANT
Blister packaged for your protection. Do not use if individual seals are broken.

Distributed by: Ciba Self-Medication, Inc.
Woodbridge, NJ 07095
Tablets made in Great Britain

Shown in Product Identification Guide, page 308

TRANSDERM SCŌP® ℞

[trans-derm scōpe]

scopolamine

Transdermal Therapeutic System

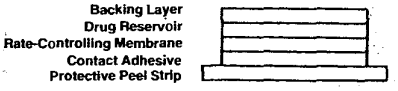
Programmed delivery in vivo of 0.5 mg of scopolamine over 3 days

Prescribing Information

DESCRIPTION

The Transderm Scōp patch is a circular flat disc designed for continuous release of scopolamine following application to an area of intact skin on the head, behind the ear. Clinical evaluation has demonstrated that the patch provides effective antiemetic and antinauseant actions when tested against motion-sickness stimuli in adults. The Transderm Scōp patch is a film 0.2 mm thick and 2.5 cm^2, with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: (1) a backing layer of tan-colored, aluminized, polyester film; (2) a drug reservoir of scopolamine, mineral oil, and polyisobutylene; (3) a microporous polypropylene membrane that controls the rate of delivery of scopolamine from the patch to the skin surface; and (4) an adhesive formulation of mineral oil, polyisobutylene, and scopolamine. A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the patch is used. The inactive components, mineral oil (12.4 mg) and polyisobutylene (11.4 mg), are not released from the system.

Cross section of the patch:



Release-Rate Concept: The Transderm Scōp patch contains 1.5 mg of scopolamine. The patch is programmed to deliver 0.5 mg of scopolamine at an approximately constant rate to the systemic circulation over the 3-day lifetime of the patch. An initial priming dose of scopolamine, released from the adhesive layer of the patch, saturates the skin binding sites and rapidly brings the plasma concentration of scopolamine to the required steady-state level. A continuous controlled release of scopolamine, which flows from the drug reservoir through the rate-controlling membrane, maintains the plasma level constant.

CLINICAL PHARMACOLOGY

The sole active agent of Transderm Scōp is scopolamine, a belladonna alkaloid with well-known pharmacological properties. The drug has a long history of oral and parenteral use for central anticholinergic activity, including prophylaxis of motion sickness. The mechanism of action of scopolamine in the central nervous system (CNS) is not definitely known but may include anticholinergic effects. The ability of scopolamine to prevent motion-induced nausea is believed to be associated with inhibition of vestibular input to the CNS, which results in inhibition of the vomiting reflex. In addition, scopolamine may have a direct action on the vomiting center within the reticular formation of the brain stem. Applied to the postauricular skin, Transderm Scōp provides for a gradual release of scopolamine from an adhesive matrix of mineral oil and polyisobutylene.

INDICATIONS AND USAGE

Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The patch should be applied only to skin in the postauricular area.

Clinical Results: Transderm Scōp provides antiemetic protection within several hours following application of the patch behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.

CONTRAINDICATIONS

Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS

Transderm Scōp should not be used in children and should be used with special caution in the elderly. See PRECAUTIONS.

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS

General

Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the patch.

Patients should be advised to remove the patch immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions

Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use

Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether the patch will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS

The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of patients on drug. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of patients on drug. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry, itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp patch. These symptoms have occurred most often in patients who have used the patches for more than three days.

OVERDOSAGE

Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp patch should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION

Initiation of Therapy: One Transderm Scōp patch (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one patch should be worn at any time.

Handling: After the patch is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the patch, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)

Continuation of Therapy: Should the patch become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first patch should be discarded, and a fresh one placed on the hairless area behind the other ear.

Disposal: The patch will still contain some active ingredient after use. To avoid accidental contact or ingestion by children or pets, fold the used patch in half with the sticky side together and dispose in the trash out of the reach of children and pets.

HOW SUPPLIED

The Transderm Scōp patch is a tan-colored disc, 2.5 cm^2, on a clear, oversized, hexagonal peel strip, which is removed prior to use.

Each Transderm Scōp patch contains 1.5 mg of scopolamine and is programmed to deliver *in vivo* 0.5 mg of scopolamine over 3 days. Transderm Scōp is available in packages of four patches. Each patch is foil wrapped. Patient instructions are included.

1 Package (4 patches) ..... NDC 0083-4345-04

The patch should be stored between 59° - 86°F (15° - 30°C).

CAUTION

Federal law prohibits dispensing without prescription.

C88-5 (Rev. 2/88)

Please read this instruction sheet carefully before opening the patch package.

Information for the Patient About—

TRANSDERM SCŌP®

Generic Name: scopolamine,
pronounced skoe-POL-a-meen

Transdermal Therapeutic System

The Transderm Scōp patch helps to prevent the nausea and vomiting of motion sickness for up to 3 days. It is an adhesive patch that you place behind your ear several hours before you travel. Wear only one patch at any time.

Be sure to wash your hands thoroughly with soap and water immediately after handling the patch, so that any drug that might get on your hands will not come into contact with your eyes.

Avoid drinking alcohol while using Transderm Scōp. Also, be careful about driving or operating any machinery while using the patch because the drug might make you drowsy.

DO NOT USE TRANSDERM SCŌP IF YOU ARE ALLERGIC TO SCOPOLAMINE OR HAVE GLAUCOMA.

TRANSDERM SCŌP SHOULD NOT BE USED IN CHILDREN AND SHOULD BE USED WITH SPECIAL CAUTION IN THE ELDERLY.

How the Transderm Scōp Patch Works

A group of nerve fibers deep inside the ear helps people keep their balance. For some people, the motion of ships, airplanes, trains, automobiles, and buses increases the activity of these nerve fibers. This increased activity causes the *dizziness, nausea, and vomiting* of motion sickness. People may have one, some, or all of these symptoms.

Transderm Scōp contains the drug scopolamine, which helps reduce the activity of the nerve fibers in the inner ear. When a Transderm Scōp patch is placed on the skin behind one of the ears, scopolamine passes through the skin and into the bloodstream. One patch may be kept in place for 3 days if needed.

Precautions

Before using Transderm Scōp be sure to tell your doctor if you—

- Are pregnant or nursing (or planning to become pregnant)
- Have (or have had) glaucoma (increased pressure in the eyeball)
- Have (or have had) any metabolic, liver, or kidney disease
- Have any obstructions of the stomach or intestine
- Have trouble urinating or any bladder obstruction
- Have any skin allergy or have had a skin reaction such as a rash or redness to any drug, especially scopolamine, or chemical or food substance.

Any of these conditions could make Transderm Scōp unsuitable for you. Also tell your doctor if you are taking any other medicines.

In the unlikely event that you experience pain in the eye and reddened whites of the eye, which may be accompanied by widening of the pupil and blurred vision, remove the patch immediately and consult your physician. As indicated below under Side Effects, widening of the pupils and blurred vision without pain or reddened whites of the eye is usually temporary and not serious.

Transderm Scōp should not be used in children. The safety of its use in children has not been determined. Children and the elderly may be particularly sensitive to the effects of scopolamine.

Side Effects

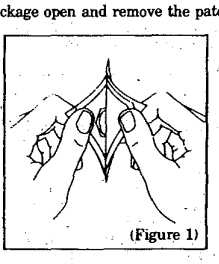
The most common side effect experienced by people using Transderm Scōp is dryness of the mouth. This occurs in about two thirds of patch users. A less frequent side effect is drowsiness, which occurs in less than one sixth of patch users. Temporary blurring of vision and dilation (widening) of the pupils may occur, especially if the drug is on your hands and comes in contact with the eyes. On infrequent occasions, disorientation, memory disturbances, dizziness, restlessness, hallucinations, confusion, difficulty urinating, skin rashes or redness, dry, itchy, or red eyes and eye pain have been reported. If these effects do occur, remove the patch and call your doctor. Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, be careful driving or operating any dangerous machinery, especially when you first start using the patch.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few people following discontinuation of the Transderm Scōp patch. These symptoms have occurred most often in people who have used patches for more than three days. We recommend that you consult your doctor if these symptoms occur.

How to Use Transderm Scōp

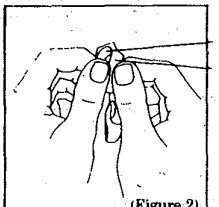
Transderm Scōp should be stored between 59° - 86°F (15° - 30°C) until you are ready to use it.

1. Plan to apply one Transderm Scōp patch at least 4 hours before you need it. **Wear only one patch at any time.**
2. Select a hairless area of skin behind one ear, taking care to avoid any cuts or irritations. Wipe the area with a clean, dry tissue.
3. Peel the package open and remove the patch (Figure 1).



(Figure 1)

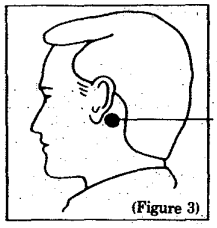
4. Remove the clear plastic six-sided backing from the patch. Try not to touch the adhesive surface on the patch with your hands (Figure 2).



(Figure 2)

5. Firmly apply the adhesive surface (metallic side) to the dry area of skin behind the ear so that the tan-colored side is showing (Figure 3). Make good contact, especially around the edge. Once you have placed the patch behind your ear, do not move it for as long as you want to use it (up to 3 days).

[See Figure at top of next column.]



(Figure 3)

6. ***Important:*** **After the patch is in place, be sure to wash your hands thoroughly with soap and water to remove any scopolamine. If this drug were to contact your eyes, it could cause temporary blurring of vision and dilation (widening) of the pupils (the dark circles in the center of your eyes). This is not serious unless accompanied by eye pain and redness (see Precautions), and your pupils should return to normal.**
7. Remove the patch after 3 days and throw it away. (You may remove it sooner if you are no longer concerned about motion sickness.) After removing the patch, be sure to wash your hands and the area behind your ear thoroughly with soap and water.
8. If you wish to control nausea for longer than 3 days, *remove* the first patch after 3 days and place a new one *behind the other ear,* repeating instructions 2 to 7.
9. Keep the patch dry, if possible, to prevent it from falling off. Limited contact with water, however, as in bathing or swimming, will not affect the system. In the unlikely event that the patch falls off, throw it away and put a new one behind the other ear.

Disposal

The patch will still contain some active ingredient after use. To avoid accidental contact or ingestion by children or pets, fold the used patch in half with the sticky side together and dispose in the trash out of the reach of children and pets.

This leaflet presents a summary of information about Transderm Scōp. If you would like more information or if you have any questions, ask your doctor or pharmacist. A more technical leaflet is available, written for your doctor. If your would like to read the leaflet, ask your pharmacist to show you a copy. You may need the help of your doctor or pharmacist to understand some of the information.

Dist. by:
Ciba Self-Medication, Inc.
Woodbridge, NJ 07095

C88-6 (Rev. 2/88)

Shown in Product Identification Guide, page 308

Colgate Oral Pharmaceuticals, Inc.

a subsidiary of Colgate-Palmolive Company
ONE COLGATE WAY
CANTON, MA 02021 U.S.A.

Direct Inquiries to:
Professional Services Department
(800) 226-5428

For Medical Information Contact:
In Emergencies:
Pittsburgh Poison Control
(412) 692-5596

LURIDE® DROPS

Brand of Sodium Fluoride

℞

DESCRIPTION

LURIDE® brand of sodium fluoride is available as liquid drops. Each ml contains 0.5 mg fluoride ion (F^-) from 1.1 mg sodium fluoride (NaF). For use as a dental caries preventive in pediatric patients. Sugar-free. Saccharin-free.

ACTIVE INGREDIENT: Sodium fluoride 0.11% (w/v).

INACTIVE INGREDIENTS: Purified water, sorbitol solution 70%, propylene glycol, methyl paraben, propyl paraben, flavor, FD&C Yellow No. 6.

CLINICAL PHARMACOLOGY

Sodium fluoride acts systemically (before tooth eruption) and topically (post-eruption) by increasing tooth resistance to acid dissolution, by promoting remineralization and by inhibiting the cariogenic microbial process.

Continued on next page

Dura—Cont.

FENESIN™
ORAL EXPECTORANT TABLET

DESCRIPTION
Each light blue, scored, sustained-release tablet provides 600 mg guaifenesin in a specially-prepared base to provide a prolonged therapeutic effect. Guaifenesin is an expectorant having the chemical name: 1,2-Propanediol, 3-(2-methoxphenoxy)-.
Inactive Ingredients: colloidal silicon dioxide, FD&C Blue #1, partially hydrogenated cottonseed oil, dicalcium phosphate, hydroxypropyl methylcellulose, magnesium stearate, stearic acid.

HOW SUPPLIED
Fenesin is available as a light blue, scored tablet embossed with DURA on one side and 009 on the other.
Bottles of 100 (NDC 51479-009-01)
Bottles of 600 (NDC 51479-009-06)
Store at room temperature, 15°–25°C (59°–77°F).
Dispense in a tight, light-resistant container (USP/NF) with a child-resistant closure.

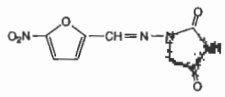
FENESIN™ DM
ANTITUSSIVE/EXPECTORANT TABLET

DESCRIPTION
Each dark blue, scored tablet for oral administration contains:
dextromethorphan hydrobromide ..... 30 mg
guaifenesin ..... 600 mg
in a special base to provide a prolonged therapeutic effect.

HOW SUPPLIED
Fenesin DM is available as a dark blue, scored tablet embossed with *Dura* on one side and *FDM 014* on the other.
Bottles of 100 (NDC 51479-014-01).
Store at controlled room temperature 15°–25°C (59°–77°F).
Dispense in a tight, light-resistant container (USP/NF) with a child-resistant closure.

FURADANTIN®
(nitrofurantoin)
Oral Suspension

DESCRIPTION
Furadantin (nitrofurantoin), a synthetic chemical, is a stable, yellow, crystalline compound. Furadantin is an antibacterial agent for specific urinary tract infections. Furadantin is available in 25 mg/5 mL liquid suspension for oral administration.



1-[[(5-nitro-2-furanyl)methylene]amino]-2, 4-imidazolidinedione

DOSAGE AND ADMINISTRATION
Furadantin should be given with food to improve drug absorption and, in some patients, tolerance.
Adults: 50–100 mg four times a day—the lower dosage level is recommended for uncomplicated urinary tract infections.
Children: 5–7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under one month of age).
The following table is based on an average weight in each range receiving 5 to 6 mg/kg of body weight per 24 hours, given in four divided doses. It can be used to calculate an average dose of Furadantin Oral Suspension (25 mg/5 mL) for children (one 5-mL teaspoon of Furadantin Oral Suspension contains 25 mg of Furadantin):

Body Weight		No. Teaspoonfuls
Pounds	Kilograms	4 Times Daily
15 to 26	7 to 11	1/2 (2.5 mL)
27 to 46	12 to 21	1 (5 mL)
47 to 68	22 to 30	1 1/2 (7.5 mL)
69 to 91	31 to 41	2 (10 mL)

Therapy should be continued for one week or for at least 3 days after sterility of the urine is obtained. Continued infection indicates the need for reevaluation.
For long-term suppressive therapy in adults, a reduction of dosage to 50–100 mg at bedtime may be adequate. For long-term suppressive therapy in children, doses as low as 1 mg/kg per 24 hours, given in a single dose or in two divided doses, may be adequate.
SEE WARNINGS SECTION REGARDING RISKS ASSOCIATED WITH LONG-TERM THERAPY.

HOW SUPPLIED
Furadantin Oral Suspension is available in:
NDC 51479-029-06 amber bottle of 60 mL
NDC 51479-029-47 amber bottle of 470 mL
Avoid exposure to strong light which may darken the drug. It is stable in storage. It should be dispensed in amber bottles.
CAUTION: Federal law prohibits dispensing without prescription.

GUAI-VENT™/PSE TABLETS

DESCRIPTION
Each Guai-Vent/PSE white, scored tablet for oral administration contains:
pseudoephedrine HCl ..... 120 mg
guaifenesin ..... 600 mg
in a special base to provide a prolonged action.

HOW SUPPLIED
Guai-Vent/PSE is available as a white, scored tablet imprinted with Dura and 015.
NDC 51479-015-01 Bottle of 100
Dispense in tight containers as defined in USP/NF.
Store between 15°–25°C (59°–77°F).
Dispense in child-resistant containers.

RONDEC® Chewable Tablets
with brompheniramine

DESCRIPTION
A scored, pink-colored, strawberry-tasting chewable tablet.
Each tablet contains:
Brompheniramine maleate ..... 4 mg
Pseudoephedrine hydrochloride ..... 60 mg
Also contains as inactive ingredients artificial strawberry flavoring aspartame, colloidal silicon dioxide, crospovidone, D&C Red #7 (calcium lake), magnesium stearate, mannitol, microcrystalline cellulose, talc, ethylcellulose, povidone K-90, and paraffin wax.
A slight color change (i.e., from pink to peach) may occur over time, but has no effect on its quality or potency.
Rondec® Chewable Tablets with brompheniramine contain ingredients of the following therapeutic classes: antihistamine and nasal decongestant.

CLINICAL PHARMACOLOGY
Brompheniramine maleate is an alkylamine-type antihistamine. This group of antihistamines is among the most active histamine antagonists and is generally effective in relatively low doses. The drugs are not so prone to produce drowsiness and are among the most suitable agents for day time use; but again, a significant proportion of patients do experience this effect. Pseudoephedrine hydrochloride is a sympathomimetic which acts predominantly on alpha receptors and has some action on beta receptors.

INDICATIONS
For the temporary relief of symptoms of seasonal and perennial allergic rhinitis, and vasomotor rhinitis.

CONTRAINDICATIONS
Hypersensitivity to any of the ingredients. Also contraindicated in patients with severe hypertension, severe coronary artery disease, patients on MAO inhibitor therapy, patients with narrow-angle glaucoma, urinary retention, peptic ulcer and during an asthmatic attack.

WARNINGS
Considerable caution should be exercised in patients with hypertension, diabetes mellitus, ischemic heart disease, hyperthyroidism, increased intraocular pressure and prostatic hypertrophy. The elderly (60 years or older) are more likely to exhibit adverse reactions.
Antihistamines may cause excitability, especially in children. At dosages higher than the recommended dose, nervousness, dizziness or sleeplessness may occur.

PRECAUTIONS
General: Caution should be exercised in patients with high blood pressure, heart disease, diabetes or thyroid disease. The antihistamine in this product may exhibit additive effects with other CNS depressants, including alcohol.
Phenylketonurics: Contains phenylalanine 30.9 mg per tablet.
Information for Patients: This antihistamine may cause drowsiness and ambulatory patients who operate machinery or motor vehicles should be cautioned accordingly. Rondec Chewable must be chewed thoroughly before swallowing.
Drug Interactions: MAO inhibitors and beta adrenergic blockers increase the effects of sympathomimetics. Sympathomimetics may reduce the antihypertensive effects of methyldopa, mecamylamine, and reserpine. Concomitant use of antihistamines with alcohol and other CNS depressants may have an additive effect.
Pregnancy: The safety of use of this product in pregnancy has not been established.
Nursing Mothers: It is not known whether the drugs in Rondec Chewable are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the product, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness of Rondec Chewable tablets in pediatric patients below the age of 6 years have not been established.

ADVERSE REACTIONS
Adverse reactions include drowsiness, lassitude, nausea, giddiness, dryness of mouth, blurred vision, cardiac palpitations, flushing, increased irrritability or excitement (especially in childen).

OVERDOSAGE
The treatment of overdosage should provide symptomatic and supportive care. Induction of emesis and gastric lavage may be performed if the patient is alert and seen within early hours after ingestion. Drug remaining in the stomach may be absorbed by the administration of activated charcoal. Stimulants should not be used because they may precipitate convulsions. If convulsions or marked CNS excitement occurs, treatment with appropriate measures is indicated.

DOSAGE AND ADMINISTRATION
Adults and adolescents 12 and over: One tablet every 4 hours not to exceed 6 doses in 24 hours. Children 6 to 12 years: One-half tablet every 4 hours not to exceed 6 doses in 24 hours.

HOW SUPPLIED
Bottles of 100 (NDC 51479-017-01). Each tablet is coded "DURA" on one side and "017" on the reverse side.
Dispense in a tight, light-resistant container as defined in USP/NF with a child-resistant closure. Store between 15°–23°C (59°–73°F).
CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION.
Manufactured for Dura Pharmaceuticals, Inc.
San Diego, CA 92121
Manufactured by Central Pharmaceuticals, Inc.
Seymour, IN 47274

RC002B0296

RONDEC®Oral Drops
RONDEC®Syrup
RONDEC®Tablet
RONDEC-TR®Tablet

DESCRIPTION
Antihistamine/Decongestant
for oral use

for infants
RONDEC®Oral Drops
each dropperful (1 mL) contains carbinoxamine maleate, 2 mg; pseudoephedrine hydrochloride, 25 mg.
Inactive Ingredients: Citric acid, DC Red No. 33, FDC Yellow No. 6, glycerin, methylparaben, propylparaben, purified water, sodium benzoate, sodium citrate, sorbitol and artificial flavoring.

for young children
RONDEC®Syrup
each teaspoonful (5 mL) contains carbinoxamine maleate, 4 mg; pseudoephedrine hydrochloride, 60 mg.
Inactive Ingredients: Citric acid, DC Red No. 33, FDC Yellow No. 6, glycerin, methylparaben, propylparaben, purified water, sodium benzoate, sodium citrate, sorbitol and artificial flavoring.

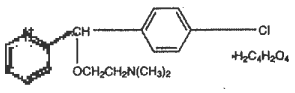
for adults and children 6 years and over
RONDEC®Tablet
each Filmtab® tablet contains carbinoxamine maleate, 4 mg; pseudoephedrine hydrochloride, 60 mg.
Inactive Ingredients: Cellulosic polymers, FDC Yellow No. 6, hydrogenated vegetable oil wax, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidine, propylene glycol, silicon dioxide, sodium starch glycolate, sorbitan monooleate, titanium dioxide and vanillin.

for adults and children 12 years and over

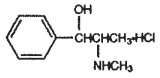
RONDEC-TR®Tablet ℞

each timed-release Filmtab tablet contains carbinoxamine maleate, 8 mg; pseudoephedrine hydrochloride, 120 mg.

Inactive Ingredients: Castor oil, cellulosic polymers, confectioner's sugar, cornstarch, FDC Blue No. 1, lactose, magnesium stearate, methyl acrylate-methyl methacrylate copolymer, microcrystalline cellulose, povidone, propylene glycol, sorbitan monooleate and titanium dioxide.



Carbinoxamine maleate (2-[p-Chloro-α-[2-(dimethylamino)ethoxy] benzyl] pyridine maleate) is one of the ethanolamine class of H_1 antihistamines.



Pseudoephedrine hydrochloride (Benzene-methanol, α-[1-(methylamino)ethyl]-, [S-(R*,R*)]-, hydrochloride) is the hydrochloride of pseudoephedrine, a naturally occurring dextrorotatory stereoisomer of ephedrine.

CLINICAL PHARMACOLOGY

Antihistaminic and decongestant actions.

Carbinoxamine maleate possesses H_1 antihistaminic activity and mild anticholinergic and sedative effects. Serum half-life for carbinoxamine is estimated to be 10 to 20 hours. Virtually no intact drug is excreted in the urine.

Pseudoephedrine hydrochloride is an oral sympathomimetic amine that acts as a decongestant to respiratory tract mucous membranes. While its vasoconstrictor action is similar to that of ephedrine, pseudoephedrine has less pressor effect in normotensive adults. Serum half-life for pseudoephedrine is 6 to 8 hours. Acidic urine is associated with faster elimination of the drug. About one-half of the administered dose is excreted in the urine.

INDICATIONS AND USAGE

For symptomatic relief of seasonal and perennial allergic rhinitis and vasomotor rhinitis.

Rondec Oral Drops, Rondec Syrup and Rondec Tablet are immediate-release dosage forms allowing titration of dose up to four times a day.

Rondec-TR Tablet utilizes a gradual-release mechanism providing approximately a 12-hour therapeutic effect, thus allowing twice-daily dosage.

CONTRAINDICATIONS

Patients with hypersensitivity or idiosyncrasy to any ingredients, patients taking monoamine oxidase (MAO) inhibitors, patients with narrow-angle glaucoma, urinary retention, peptic ulcer, severe hypertension or coronary artery disease, or patients undergoing an asthmatic attack.

WARNINGS

Use in Pregnancy: Safety for use during pregnancy has not been established.

Nursing Mothers: Use with caution in nursing mothers.

Special Risk Patients: Use with caution in patients with hypertension or ischemic heart disease, and persons older than 60 years.

PRECAUTIONS

Use with caution in patients with hypertension, heart disease, asthma, hyperthyroidism, increased intraocular pressure, diabetes mellitus and prostatic hypertrophy.

Information for Patients: Avoid alcohol and other CNS depressants while taking these products. Patients sensitive to antihistamines may experience moderate to severe drowsiness. Patients sensitive to sympathomimetic amines may note mild CNS stimulation. While taking these products, exercise care in driving or operating appliances, machinery, etc.

Drug Interactions: Antihistamines may enhance the effects of tricyclic antidepressants, barbiturates, alcohol, and other CNS depressants. MAO inhibitors prolong and intensify the anticholinergic effects of antihistamines. Sympathomimetic amines may reduce the antihypertensive effects of reserpine, veratrum alkaloids, methyldopa and mecamylamine. Effects of sympathomimetics are increased with MAO inhibitors and beta-adrenergic blockers.

Pregnancy Category C.: Animal reproduction studies have not been conducted with these products. It is also not known whether these products can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Give to pregnant women only if clearly needed.

ADVERSE REACTIONS

Antihistamines: Sedation, dizziness, diplopia, vomiting, diarrhea, dry mouth, headache, nervousness, nausea, anorexia, heartburn, weakness, polyuria and dysuria and, rarely, excitability in children.

Sympathomimetic Amines: Convulsions, CNS stimulation, cardiac arrhythmias, respiratory difficulty, increased heart rate or blood pressure, hallucinations, tremors, nervousness, insomnia, weakness, pallor and dysuria.

OVERDOSAGE

No information is available as to specific results of an overdose of these products. The signs, symptoms and treatment described below are those of H_1 antihistamines and ephedrine overdose.

Symptoms: Should antihistamine effects predominate, central action constitutes the greatest danger. In the small child, symptoms include excitation, hallucination, ataxia, incoordination, tremors, flushed face and fever. Convulsions, fixed and dilated pupils, coma and death may occur in severe cases. In the adult, fever and flushing are uncommon; excitement leading to convulsions and postictal depression is often preceded by drowsiness and coma. Respiration is usually not seriously depressed; blood pressure is usually stable.

Should sympathomimetic symptoms predominate, central effects include restlessness, dizziness, tremor, hyperactive reflexes, talkativeness, irritability and insomnia. Cardiovascular and renal effects include difficulty in micturition, headache, flushing, palpitation, cardiac arrhythmias, hypertension with subsequent hypotension and circulatory collapse. Gastrointestinal effects include dry mouth, metallic taste, anorexia, nausea, vomiting, diarrhea and abdominal cramps.

Treatment: a) Evacuate stomach as condition warrants. Activated charcoal may be useful. *b)* Maintain a nonstimulating environment. *c)* Monitor cardiovascular status. *d)* Do not give stimulants. *e)* Reduce fever with cool sponging. *f)* Support respiration. *g)* Use sedatives or anticonvulsants to control CNS excitation and convulsions. *h)* Physostigmine may reverse anticholinergic symptoms. *i)* Ammonium chloride may acidify the urine to increase excretion of pseudoephedrine. *j)* Further care is symptomatic and supportive.

DOSAGE AND ADMINISTRATION

AGE	DOSE*	FREQUENCY*
Rondex Oral Drops for oral use only		
1–3 months	¼ dropperful (¼ mL)	q.i.d.
3–6 months	½ dropperful (½ mL)	q.i.d.
6–9 months	¾ dropperful (¾ mL)	q.i.d.
9–18 months	1 dropperful (1 mL)	q.i.d.
Rondex Syrup and Rondec Tablet		
18 months–6 years	½ teaspoonful (2.5 mL)	q.i.d.
adults and children 6 years and over	1 teaspoonful (5 mL) or 1 tablet	q.i.d.
Rondec-TR Tablet		
adults and children 12 years and over	1 tablet	b.i.d.

*In mild cases or in particularly sensitive patients, less frequent or reduced doses may be adequate.

HOW SUPPLIED

Rondec Oral Drops, berry-flavored, in 30-mL bottles for dropper dosage, **NDC** 0074-5783-30. Calibrated shatterproof dropper enclosed in each carton. Container meets safety closure requirements.

Rondec Syrup, berry-flavored, in 16-fl-oz (1-pint) bottles, **NDC** 0074-5782-16; and 4-fl-oz bottles, **NDC** 0074-5782-04. Dispense in USP tight glass container.

Rondec Tablet, Filmtab tablets, in bottles of 100, **NDC** 0074-5726-13; and bottles of 500, **NDC** 0074-5726-53. Each orange-colored tablet marked with Ross and the number 5726 for professional identification. Dispense in USP tight container.

Rondec-TR Tablet, Filmtab tablets, in bottles of 100, **NDC** 0074-6240-13. Each blue-colored tablet marked with Ross and the number 6240 for professional identification. Dispense in USP tight container.

Recommended storage: Store below 86°F (30°C).

Revised: October, 1991

Formerly distributed by
Ross Laboratories
(division of Abbott).

Now distributed by
Dura Pharmaceuticals.

RONDEC®-DM Syrup ℞

RONDEC®-DM Oral Drops ℞

DESCRIPTION

Antihistamine/Decongestant/ Antitussive for oral use

for adults and children

RONDEC®-DM Syrup ℞

each teaspoonful (5 mL) contains carbinoxamine maleate, 4 mg; pseudoephedrine hydrochloride, 60 mg; dextromethorphan hydrobromide, 15 mg.

Inactive Ingredients: Citric acid, DC Red No. 33, FDC Blue No. 1, glycerin, menthol, purified water, sodium benzoate, sodium citrate, sorbitol, natural and artificial flavoring and other ingredients.

for infants

RONDEC®-DM Oral Drops ℞

each dropperful (1 mL) contains carbinoxamine maleate, 2 mg; pseudoephedrine hydrochloride, 25 mg; dextromethorphan hydrobromide, 4 mg.

Inactive Ingredients: Citric acid, DC Red No. 33, FDC Blue No. 1, glycerin, menthol, purified water, sodium benzoate, sodium citrate, sorbitol, natural and artificial flavoring and other ingredients.

DOSAGE AND ADMINISTRATION

AGE	DOSE*	FREQUENCY*
Rondec-DM Syrup		
18 months–6 years	½ teaspoonful (2.5 mL)	q.i.d.
adults and children 6 years and over	1 teaspoonful (5 mL)	q.i.d.
Rondec-DM Oral Drops for oral use only		
1–3 months	¼ dropperful (¼mL)	q.i.d.
3–6 months	½ dropperful (½mL)	q.i.d.
6–9 months	¾ dropperful (¾mL)	q.i.d.
9–18 months	1 dropperful (1 mL)	q.i.d.

*In mild cases or in particularly sensitive patients, less frequent of reduced doses may be adequate.

HOW SUPPLIED

Rondec-DM Syrup, grape-flavored, in 16-fl-oz (1-pint) bottles, **NDC** 0074-5640-16; and 4-fl-oz bottles, **NDC** 0074-5640-04. Dispense in USP tight, light-resistant, glass container. Avoid exposure to excessive heat.

Rondec-DM Oral Drops, grape-flavored, in 30-mL bottles for dropper dosage. Calibrated, shatterproof dropper enclosed in each carton. Container meets safety closure requirements **NDC** 0074-5639-30. Avoid exposure to excessive heat.

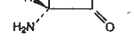
SEROMYCIN® ℞

CYCLOSERINE CAPSULES, USP

DESCRIPTION

Seromycin® (Cycloserine Capsules, USP), 3-isoxazolidinone, 4-amino-, (R)- is a broad spectrum antibiotic that is produced by a strain of *Streptomyces orchidaceus* and has also been synthesized. Cycloserine is a white to off-white powder that is soluble in water and stable in alkaline solution. It is rapidly destroyed at a neutral or acid pH.

Cycloserine has a pH between 5.5 and 6.5 in a solution containing 100 mg/mL. The molecular weight of cycloserine is 102.09, and it has an empirical formula of $C_3H_6N_2O_2$. The structural formula of cycloserine is as follows:



Each capsule contains cycloserine, 250 mg (2.45 mmol); D & C Yellow No. 10, F D & C Blue No. 1, F D & C Red No. 3, F D & C Yellow No. 6, gelatin, iron oxide, talc, titanium dioxide, and other inactive ingredients.

CLINICAL PHARMACOLOGY

After oral administration cycloserine is readily absorbed from the gastrointestinal tract, with peak blood levels occurring in 4 to 8 hours. Blood levels of 25 to 30 μg/mL can generally be maintained with the usual dosage of 250 mg twice a day, although the relationship of plasma levels to dosage is not always consistent. Concentrations in the cerebrospinal fluid, pleural fluid, fetal blood, and mother's milk approach those found in the serum. Detectable amounts are found in ascitic fluid, bile sputum, amniotic fluid, and lung and lymph tissues. Approximately 65% of a single dose of cycloserine can be recovered in the urine within 72 hours ofter oral administration. The remaining 35% is apparently metabolized to unknown substances. The maximum excretion rate occurs 2 to 6 hours after administration, with 50% of the drug eliminated in 12 hours.

Continued on next page

Janssen Pharmaceutica—Cont.

DOSAGE GUIDELINES
DOSAGE SHOULD BE INDIVIDUALIZED AND TITRATED

FOR USE DURING GENERAL ANESTHESIA

SPONTANEOUSLY BREATHING/ ASSISTED VENTILATION	**Induction of Analgesia:** 8–20 mcg/kg **Maintenance of Analgesia:** 3–5 mcg/kg q 5–20 min or 0.5 to 1 mcg/kg/min **Total dose:** 8–40 mcg/kg
ASSISTED OR CONTROLLED VENTILATION	
Incremental Injection *(To attenuate response to laryngoscopy and intubation)*	**Induction of Analgesia:** 20–50 mcg/kg **Maintenance of Analgesia:** 5–15 mcg/kg q 5–20 min **Total dose:** Up to 75 mcg/kg
Continuous Infusion *(To provide attenuation of response to intubation and incision)*	Infusion rates are variable and should be titrated to the desired clinical effect. SEE INFUSION DOSAGE GUIDELINES BELOW. **Induction of Analgesia:** 50–75 mcg/kg **Maintenance of Analgesia:** 0.5 to 3 mcg/kg/min (Average rate 1 to 1.5 mcg/kg/min) **Total dose:** Dependent on duration of procedure
Anesthetic Induction	**Induction of Anesthesia:** 130–245 mcg/kg **Maintenance of Anesthesia:** 0.5 to 1.5 mcg/kg/min or general anesthetic **Total dose:** Dependent on duration of procedure *At these doses, truncal rigidity should be expected and a muscle relaxant should be utilized.* *Administer slowly (over 3 minutes).* Concentration of inhalation agents reduced by 30–50% for initial hour.
MONITORED ANESTHESIA CARE (MAC) *(For sedated and responsive, spontaneously breathing patients)*	**Induction of MAC:** 3–8 mcg/kg **Maintenance of MAC:** 3–5 mcg/kg q 5–20 min or 0.25 to 1 mcg/kg/min **Total dose:** 3–40 mcg/kg

INFUSION DOSAGE

Continuous Infusion: 0.5–3mcg/kg/min administered with nitrous oxide/oxygen in patients undergoing general surgery. Following an anesthetic induction dose of ALFENTA, infusion rate requirements are reduced by 30–50% for the first hour of maintenance.

Changes in vital signs that indicate a response to surgical stress or lightening of anesthesia may be controlled by increasing the alfentanil to a maximum of 4 mcg/kg/min and/or administration of bolus doses of 7 mcg/kg. If changes are not controlled after three bolus doses given over a five minute period, a barbiturate, vasodilator, and/or inhalation agent should be used. Infusion rates should always be adjusted downward in the absence of these signs until there is some response to surgical stimulation.

Rather than an increase in infusion rate, 7 mcg/kg bolus doses of ALFENTA or a potent inhalation agent should be administered in response to signs of lightening of anesthesia within the last 15 minutes of surgery. ALFENTA infusion should be discontinued at least 10–15 minutes prior to the end of surgery.

tion as the analgesic component for monitored anesthesia care (MAC).

[See table above.]

Usage in Children: Clinical data to support the use of ALFENTA in patients under 12 years of age are not presently available. Therefore, such use is not recommended.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS sections).

In patients administered anesthetic (induction) dosages of ALFENTA, it is essential that qualified personnel and adequate facilities are available for the management of intraoperative and postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of ALFENTA accurately, the use of a tuberculin syringe or equivalent is recommended.

The physical and chemical compatibility of ALFENTA have been demonstrated in solution with normal saline, 5% dextrose in normal saline, 5% dextrose in water and Lactated Ringers. Clinical studies of ALFENTA infusion have been conducted with ALFENTA diluted to a concentration range of 25 mcg/mL to 80 mcg/ml.

As an example of the preparation of ALFENTA for infusion, 20 mL of ALFENTA added to 230 mL of diluent provides a 40 μg/mL solution of ALFENTA.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

SAFETY AND HANDLING

ALFENTA (alfentanil hydrochloride) is supplied in individually sealed dosage forms which pose no known risk to healthcare providers having incidental contact. Accidental dermal exposure to ALFENTA should be treated by rinsing the affected area with water.

Protect from light. Store at room temperature 15°–30°C (59°–86°F).

HOW SUPPLIED

Each mL of ALFENTA (alfentanil hydrochloride) Injection for intravenous use contains alfentanil hydrochloride equivalent to 500 μg of alfentanil base. ALFENTA Injection is available as:

NDC 50458-060-02, 2 mL ampoules in packages of 10
NDC 50458-060-05, 5 mL ampoules in packages of 10
NDC 50458-060-10, 10 mL ampoules in packages of 5
NDC 50458-060-20, 20 mL ampoules in packages of 5

U.S. Patent No. 4,167,574

April 1995, May 1995

JANSSEN PHARMACEUTICA INC.
Titusville, NJ 08560-0200

Shown in Product Identification Guide, page 318

DURAGESIC® Ⓒ Ⓡ

[dūr-a-jē'sik]

(fentanyl transdermal system)

Full Prescribing Information

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC IS CONTRAINDICATED:

- In the management of acute or post-operative pain, including use in out-patient surgeries
- In the management of mild or intermittent pain responsive to PRN or non-opioid therapy
- In doses exceeding 25 mcg/hour at the initiation of opioid therapy

(See CONTRAINDICATIONS for further information.)

DURAGESIC SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING. (See PRECAUTIONS - Pediatric Use.)

DURAGESIC is indicated for treatment of chronic pain (such as that of malignancy) that:

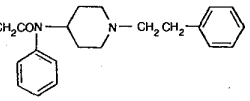
- cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids and
- requires continuous opioid administration.

The 50, 75, and 100 mcg/hour dosages should ONLY be used in patients who are already on and are tolerant to opioid therapy.

WARNING: May be habit forming.

DESCRIPTION

DURAGESIC is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. The chemical name is N-Phenyl-N-(1-2-phenylethyl-4-piperidyl) propanamide. The structural formula is



The molecular weight of fentanyl base is 336.5, and the empirical formula is $C_{22}H_{28}N_2O$. The n-octanol:water partition coefficient is 860:1. The pKa is 8.4.

System Components and Structure

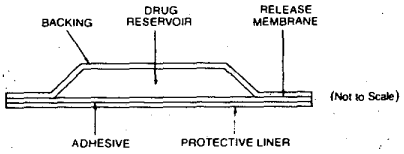
The amount of fentanyl released from each system per hour is proportional to the surface area (25 μg/h per 10 cm^2). The composition per unit area of all system sizes is identical. Each system also contains 0.1 mL of alcohol USP per 10 cm^2.

Dose* (μg/h)	Size (cm^2)	Fentanyl Content (mg)
25	10	2.5
50**	20	5
75**	30	7.5
100**	40	10

*Nominal delivery rate per hour
**FOR USE ONLY IN OPIOID TOLERANT PATIENTS

DURAGESIC is a rectangular transparent unit comprising a protective liner and four functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:

1) a backing layer of polyester film; 2) a drug reservoir of fentanyl and alcohol USP gelled with hydroxyethyl cellulose; 3) an ethylene-vinyl acetate copolymer membrane that controls the rate of fentanyl delivery to the skin surface; and 4) a fentanyl containing silicone adhesive. Before use, a protective liner covering the adhesive layer is removed and discarded.



The active component of the system is fentanyl. The remaining components are pharmacologically inactive. Less than 0.2 mL of alcohol is also released from the system during use. Do not cut or damage DURAGESIC. If the DURAGESIC system is cut or damaged, controlled drug delivery will not be possible.

CLINICAL PHARMACOLOGY

Pharmacology

Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid μ-receptor. These μ-binding sites are discretely distributed in the human brain, spinal cord, and other tissues.

In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system. Its primary actions of therapeutic value are analgesia and sedation. Fentanyl may increase the patient's tolerance for pain and decrease the perception of suffering, although the presence of the pain itself may still be recognized.

In addition to analgesia, alterations in mood, euphoria and dysphoria, and drowsiness commonly occur. Fentanyl depresses the respiratory centers, depresses the cough reflex, and constricts the pupils. Analgesic blood levels of fentanyl may cause nausea and vomiting directly by stimulating the chemoreceptor trigger zone, but nausea and vomiting are significantly more common in ambulatory than in recumbent patients, as is postural syncope.

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening rather than relief of pain.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some

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[See table A below.]
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IV Fentanyl
Surgical Patients
Hepatically Impair
Renally Impaired
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DURAGESIC 50 μg/
DURAGESIC 75 μg/
DURAGESIC 100 μg

†Estimated
*After system remov
fall 50%, on averag

cases producing urinary urgency, in others, difficulty in urination.

At therapeutic dosages, fentanyl usually does not exert major effects on the cardiovascular system. However, some patients may exhibit orthostatic hypotension and fainting.

Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl administration. Assays in man show no clinically significant histamine release in dosages up to 50 μg/kg.

Pharmacokinetics (see table and graph)

DURAGESIC releases fentanyl from the reservoir at a nearly constant amount per unit time. The concentration gradient existing between the saturated solution of drug in the reservoir and the lower concentration in the skin drives drug release. Fentanyl moves in the direction of the lower concentration at a rate determined by the copolymer release membrane and the diffusion of fentanyl through the skin layers. While the actual rate of fentanyl delivery to the skin varies over the 72 hour application period, each system is labeled with a nominal flux which represents the average amount of drug delivered to the systemic circulation per hour across average skin.

While there is variation in dose delivered among patients, the nominal flux of the systems (25, 50, 75, and 100 μg of fentanyl per hour) are sufficiently accurate as to allow individual titration of dosage for a given patient. The small amount of alcohol which has been incorporated into the system enhances the rate of drug flux through the rate-limiting copolymer membrane and increases the permeability of the skin to fentanyl.

Following DURAGESIC application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. Serum fentanyl concentrations increase gradually following initial DURAGESIC application, generally leveling off between 12 and 24 hours and remaining relatively constant, with some fluctuation, for the remainder of the 72 hour application period. Peak serum levels of fentanyl generally occurred between 24 and 72 hours after initial application. Serum fentanyl concentrations achieved are proportional to the DURAGESIC delivery rate. With continuous use, serum fentanyl concentrations continue to rise for the first few system applications. After several sequential 72-hour applications, patients reach and maintain a steady state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl (see graph and Table A).

After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 17 (range 13–22) hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life ranges from 3–12 hours.

[See graph above.]

[See table A below.]

Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. Fentanyl accumulates in the skeletal muscle and fat and is released slowly into the blood.

The average volume of distribution for fentanyl is 6 L/kg (range 3–8, N=8). The average clearance in patients undergoing various surgical procedures is 46 L/h (range 27–75, N=8). The kinetics of fentanyl in geriatric patients has not been well studied, but in geriatric patients the clearance of IV fentanyl may be reduced and the terminal half-life greatly prolonged (see PRECAUTIONS).

Fentanyl is metabolized primarily in the liver. In humans the drug appears to be metabolized primarily by N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites. Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13 and 21%. Skin does not appear to metabolize fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

Pharmacodynamics

Analgesia

DURAGESIC is a strong opioid analgesic. In controlled clinical trials in non-opioid tolerant patients, 60 mg/day IM morphine was considered to provide analgesia approximately equivalent to DURAGESIC 100 μg/h in an acute pain model. Minimum effective analgesic serum concentrations of fentanyl in opioid naive patients range from 0.2 to 1.2 ng/mL; side effects increase in frequency at serum levels above 2 ng/mL. Both the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance. The rate of development of tolerance varies widely among individuals.

Ventilatory Effects

At equivalent analgesic serum concentrations, fentanyl and morphine produce a similar degree of hypoventilation. A small number of patients have experienced clinically significant hypoventilation with DURAGESIC. Hypoventilation was manifest by respiratory rates of less than 8 breaths/minute or a pCO_2 greater than 55 mm Hg. In clinical trials of 357 postoperative (acute pain) patients treated with DURAGESIC, 13 patients experienced hypoventilation. As a consequence, 10 of these 13 patients received naloxone, two patients had their dose reduced and one patient required no treatment beyond verbal stimulation. Of the 13 events, seven were associated with DURAGESIC 100 μg/h and six were associated with DURAGESIC 75 μg/h. In these studies the incidence of hypoventilation was higher in nontolerant women (10) than in men (3) and in patients weighing less than 63 kg (9 of 13). Although patients with impaired respiration were not common in the trials, they had higher rates of hypoventilation.

While most patients using DURAGESIC chronically develop tolerance to fentanyl induced hypoventilation, episodes of slowed respirations may occur at any time during therapy; medical intervention generally was not required in these instances.

Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations. However, the risk of hypoventilation increases at serum fentanyl concentrations greater than 2 ng/mL in non opioid-tolerant patients, especially for patients who have an underlying pulmonary condition or who receive usual doses of opioids or other CNS drugs associated with hypoventilation in addition to DURAGESIC. The use of DURAGESIC should be monitored by clinical evaluation. As with other drug level measurements, serum fentanyl concentrations may be useful clinically, although they do not reflect patient sensitivity to fentanyl and should not be used by physicians as a sole indicator of effectiveness or toxicity.

See BOX WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE for additional information on hypoventilation.

Cardiovascular Effects

Intravenous fentanyl may infrequently produce bradycardia. The incidence of bradycardia in clinical trials with DURAGESIC was less than 1%.

CNS Effects

In opioid naive patients, central nervous system effects increase when serum fentanyl concentrations are greater than 3 ng/mL.

CLINICAL TRIALS

DURAGESIC was studied in patients with acute and chronic pain (postoperative and cancer pain models).

The analgesic efficacy of DURAGESIC was demonstrated in an acute pain model with surgical procedures expected to produce various intensities of pain (eg hysterectomy, major orthopedic surgery). Clinical use and safety was evaluated in patients experiencing chronic pain due to malignancy. Based on the results of these trials, DURAGESIC was determined to be effective in both populations, but safe only for use in patients with chronic pain. Because of the risk of hypoventilation (4% incidence) in postoperative patients with actue pain, DURAGESIC is contraindicated for postoperative analgesia. (See BOX WARNING and CONTRAINDICATIONS.)

DURAGESIC as therapy for pain due to cancer has been studied in 153 patients. In this patient population, DURAGESIC has been administered in doses of 25 μg/h to 600 μg/h. Individual patients have used DURAGESIC continuously for up to 866 days. At one month after initiation of

Continued on next page

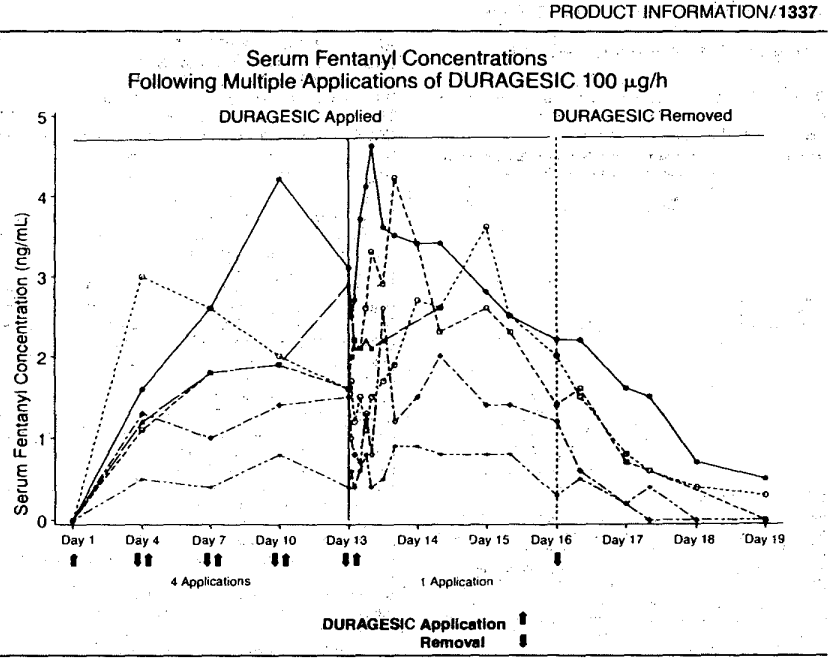


TABLE A
RANGE OF PHARMACOKINETIC PARAMETERS OF FENTANYL IN PATIENTS

	Clearance (L/h) Range (70 kg)	Volume of Distribution V_{SS} (L/kg) Range	Half Life $t_{1/2}$ (h) Range	Maximal Concentration C_{max} (ng/mL) Range	Time to Maximal Concentration (h) Range
IV Fentanyl					
Surgical Patients	27–75	3–8	3–12		
Hepatically Impaired Patients	3–80†	0.8–8†	4–12†		
Renally Impaired Patients	30–78				
DURAGESIC 25 μg/h			*	0.3–1.2	26–78
DURAGESIC 50 μg/h			*	0.6–1.8†	24–72†
DURAGESIC 75 μg/h			*	1.1–2.6	24–48
DURAGESIC 100 μg/h			*	1.9–3.8	25–72

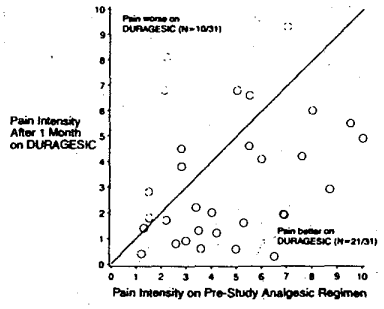
†Estimated

*After system removal there is continued systemic absorption from residual fentanyl in the skin so that serum concentrations fall 50%, on average, in 17 hours.

Janssen Pharmaceutica—Cont.

DURAGESIC therapy, patients generally reported lower pain intensity scores as compared to a prestudy analgesic regimen of oral morphine (see graph)

Visual Analogue Score of Pain Intensity Ratings at Entry in the Study and After One Month of DURAGESIC Use



INDICATIONS AND USAGE

DURAGESIC is indicated in the management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids.

DURAGESIC should not be used in the management of acute or postoperative pain because serious or life-threatening hypoventilation could result. (See BOX WARNING and CONTRAINDICATIONS.)

In patients with chronic pain, it is possible to individually titrate the dose of the transdermal system to minimize the risk of adverse effects while providing analgesia. In properly selected patients, DURAGESIC is a safe and effective alternative to other opioid regimens. (See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC IS CONTRAINDICATED:

- **in the management of acute or post-operative pain, including use in out-patient surgeries because there is no opportunity for proper dose titration (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION),**
- **in the management of mild or intermittent pain that can otherwise be managed by lesser means such as acetaminophen-opioid combinations, non-steriodal analgesics, or PRN dosing with short-acting opioids, and**
- **in doses exceeding 25 mcg/hour at the initiation of opioid therapy because of the need to individualize dosing by titrating to the desired analgesic effect.**

DURAGESIC is also contraindicated in patients with known hypersensitivity to fentanyl or adhesives.

WARNINGS

DURAGESIC SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING. (See PRECAUTIONS-Pediatric Use.)

PATIENTS WHO HAVE EXPERIENCED ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 12 HOURS AFTER DURAGESIC REMOVAL SINCE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND REACH AN APPROXIMATE 50% REDUCTION IN SERUM CONCENTRATIONS 17 HOURS AFTER SYSTEM REMOVAL.

DURAGESIC SHOULD BE PRESCRIBED ONLY BY PERSONS KNOWLEDGEABLE IN THE CONTINUOUS ADMINISTRATION OF POTENT OPIOIDS, IN THE MANAGEMENT OF PATIENTS RECEIVING POTENT OPIOIDS FOR TREATMENT OF PAIN, AND IN THE DETECTION AND MANAGEMENT OF HYPOVENTILATION INCLUDING THE USE OF OPIOID ANTAGONISTS.

THE CONCOMITANT USE OF OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS, INCLUDING OTHER OPIOIDS, SEDATIVES OR HYPNOTICS, GENERAL ANESTHETICS, PHENOTHIAZINES, TRANQUILIZERS, SKELETAL MUSCLE RELAXANTS, SEDATING ANTIHISTAMINES, AND ALCOHOLIC BEVERAGES MAY PRODUCE ADDITIVE DEPRESSANT EFFECTS. HYPOVENTILATION, HYPOTENSION AND PROFOUND SEDATION OR COMA MAY OCCUR. WHEN SUCH COMBINED THERAPY IS CONTEMPLATED, THE DOSE OF ONE OR BOTH AGENTS SHOULD BE REDUCED BY AT LEAST 50%.

ALL PATIENTS SHOULD BE ADVISED TO AVOID EXPOSING THE DURAGESIC APPLICATION SITE TO DIRECT EXTERNAL HEAT SOURCES, SUCH AS HEATING PADS OR ELECTRIC BLANKETS, HEAT LAMPS, SUANAS, HOT TUBS, AND HEATED WATER BEDS, ETC. WHILE WEARING THE SYSTEM. THERE IS A POTENTIAL FOR TEMPERATURE-DEPENDENT INCREASES IN FENTANYL RELEASE FROM THE SYSTEM. (See PRECAUTIONS, Patients with Fever/External Heat.)

PRECAUTIONS

General

DURAGESIC doses greater than 25 μg/h are too high for initiation of therapy in non opioid-tolerant patients and should not be used to begin DURAGESIC therapy in these patients. (See BOX WARNING.)

DURAGESIC may impair mental and/or physical ability required for the performance of potentially hazardous tasks (eg driving, operating machinery). Patients who have been given DURAGESIC should not drive or operate dangerous machinery unless they are tolerant to the side effects of the drug.

Patients should be instructed to keep both used and unused systems out of the reach of children. Used systems should be folded so that the adhesive side of the system adheres to itself and flushed down the toilet immediately upon removal. Patients should be advised to dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused systems should be removed from their pouch and flushed down the toilet.

Hypoventilation (Respiratory Depression)

Hypoventilation may occur at any time during the use of DURAGESIC.

Because significant amounts of fentanyl are absorbed from the skin for 17 hours or more after the system is removed, hypoventilation may persist beyond the removal of DURAGESIC. Consequently, patients with hypoventilation should be carefully observed for degree of sedation and their respiratory rate monitored until respiration has stabilized. The use of concomitant CNS active drugs requires special patient care and observation. See WARNINGS.

Chronic Pulmonary Disease

Because potent opioids can cause hypoventilation, DURAGESIC® (fentanyl transdermal system) should be administered with caution to patients with preexisting medical conditions predisposing them to hypoventilation. In such patients, normal analgesic doses of opioids may further decrease respiratory drive to the point of respiratory failure.

Head Injuries and Increased Intracranial Pressure

DURAGESIC should not be used in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. DURAGESIC should be used with caution in patients with brain tumors.

Cardiac Disease

Intravenous fentanyl may produce bradycardia. Fentanyl should be administered with caution to patients with bradyarrhythmias.

Hepatic or Renal Disease

At the present time insufficient information exists to make recommendations regarding the use of DURAGESIC in patients with impaired renal or hepatic function. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

Patients with Fever/External Heat

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one third for patients with a body temperature of 40°C (102°F) due to temperature-dependent increases in fentanyl release from the system and increased skin permeability. Therefore, patients wearing DURAGESIC systems who develop fever should be monitored for opioid side effects and the DURAGESIC dose should be adjusted if necessary.

ALL PATIENTS SHOULD BE ADVISED TO AVOID EXPOSING THE DURAGESIC APPLICATION SITE TO DIRECT EXTERNAL HEAT SOURCES, SUCH AS HEATING PADS OR ELECTRIC BLANKETS, HEAT LAMPS, SAUNAS, HOT TUBS, AND HEATED WATER BEDS, ETC. WHILE WEARING THE SYSTEM. THERE IS A POTENTIAL FOR TEMPERATURE-DEPENDENT INCREASES IN FENTANYL RELEASE FROM THE SYSTEM.

Central Nervous System Depressants

When patients are receiving DURAGESIC, the dose of additional opioids or other CNS depressant drugs (including benzodiazepines) should be reduced by at least 50%. With the concomitant use of CNS depressants, hypotension may occur.

Drug or Alcohol Dependence

Use of DURAGESIC in combination with alcoholic beverages and/or other CNS depressants can result in increased risk to the patient. DURAGESIC should be used with caution in individuals who have a history of drug or alcohol abuse, especially if they are outside a medically controlled environment.

Ambulatory Patients

Strong opioid analgesics impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients who have been given DURAGESIC should not drive or operate dangerous machinery unless they are tolerant to the effects of the drug.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Because long-term animal studies have not been conducted, the potential carcinogenic effects of DURAGESIC are unknown. There was no evidence of mutagenicity in the Ames Salmonella mutagenicity assay, the primary rat hepatocyte unscheduled DNA synthesis assay, the BALB/c-3T3 transformation test, and the human lymphocyte and CHO chromosomal aberration in-vitro assays.

In the mouse lymphoma assay, fentanyl concentrations 2000 times greater than those seen with chronic DURAGESIC use were only mutagenic in the presence of metabolic activation.

Pregnancy—Pregnancy Category C

Fentanyl has been shown to impair fertility and to have an embryocidal effect in rats when given in intravenous doses 0.3 times the human dose for a period of 12 days. No evidence of teratogenic effects has been observed after administration of fentanyl to rats. There are no adequate and well-controlled studies in pregnant women. DURAGESIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

DURAGESIC is not recommended for analgesia during labor and delivery.

Nursing Mothers

Fentanyl is excreted in human milk; therefore DURAGESIC is not recommended for use in nursing women because of the possibility of effects in their infants.

Pediatric Use

The safety and efficacy of DURAGESIC in children has not been established. (See BOX WARNING and CONTRAINDICATIONS.)

DURAGESIC SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING.

Geriatric Use

Information from a pilot study of the pharmacokinetics of IV fentanyl in geriatric patients indicates that the clearance of fentanyl may be greatly decreased in the population above the age of 60. The relevance of these findings to transdermal fentanyl is unknown at this time.

Since elderly, cachectic, or debilitated patients may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance, they should not be started on DURAGESIC doses higher than 25 μg/h unless they are already taking more than 135 mg of oral morphine a day or an equivalent dose of another opioid (see DOSAGE AND ADMINISTRATION).

Information for Patients

Instructions for the application, removal, and disposal of DURAGESIC are provided in each carton.

Disposal of DURAGESIC

DURAGESIC should be kept out of the reach of children. DURAGESIC systems should be folded so that the adhesive side of the system adheres to itself, then the system should be flushed down the toilet immediately upon removal. Patients should dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused systems should be removed from their pouch and flushed down the toilet. If the gel from the drug reservoir accidentally contacts the skin, the area should be washed with clear water.

ADVERSE REACTIONS

In post-marketing experience, deaths from hypoventilation due to inappropriate use of DURAGESIC have been reported. (See BOX WARNING and CONTRAINDICATIONS.)

Pre-marketing Clinical Trial Experience:

The safety of DURAGESIC has been evaluated in 357 postoperative patients and 153 cancer patients for a total of 510 patients. Patients with acute pain used DURAGESIC for 1 to 3 days. The duration of DURAGESIC use varied in cancer patients; 56% of patients used DURAGESIC for over 30 days, 28% continued treatment for more than 4 months, and 10% used DURAGESIC for more than 1 year.

Hypoventilation was the most serious adverse reaction observed in 13 (4%) postoperative patients and in 3 (2%) of the cancer patients. Hypotension and hypertension were observed in 11 (3%) and 4 (1%) of the opioid-naive patients.

Various adverse events were reported; a causal relationship to DURAGESIC was not always determined. The frequencies presented here reflect the actual frequency of each adverse effect in patients who received DURAGESIC. There has been no attempt to correct for a placebo effect, concomitant use of other opioids, or to subtract the frequencies reported by placebo-treated patients in controlled trials.

The following adverse reactions were reported in 153 cancer patients at a frequency of 1% or greater; similar reactions were seen in the 357 postoperative patients studied.

Body as a Whole: a
Cardiovascular: arr
Digestive: nausea**, mouth**, anorexia*,
Nervous: somnolen ness*, nervousness*, euphoria*, tremor, al abnormal thinking, a tion, paresthesia, am
Respiratory: dyspne sis, pharyngitis, hicc
Skin and Appendage cation site reaction -
Urogenital: urinary
*Reactions occurrin
**Reactions occurri patients

The following adverse 1% of the 510 postope association between t tration is unknown. alerting information
Digestive: abdomin
Nervous: aphasia, l depersonalization, hc
Respiratory: stertor disorder
Skin and Appendag pustules
Special Senses: aml
Urogenital: bladder

DRUG ABUSE AN

Fentanyl is a Schedu duce drug dependenc DURAGESIC therefc ance, physical and p upon repeated admi tion following opioid a cians should not let them from using adeq ment of severe pain

OVERDOSAGE

Clinical Presentation

The manifestations o of its pharmacologic a effect being hypoven

Treatment

For the management measures include re physically or verbally can be followed by ac tagonist such as nalo following an overdos narcotic antagonist's from 30 to 81 minute doses should be carefu re-narcotization after tion of naloxone may effect may result in catecholamines.

If the clinical situatic established and main control respiration a airway or endotrach temperature and flui

If severe or persisten hypovolemia should b priate parenteral flui

DOSAGE AND AD

With all opioids, the dependent on health strict conformity wit to patient selection, As with all opioids, most important facto appropriate dose is t ance. (See BOX WAR Initial doses should patients (see PRECA DURAGESIC should irradiated skin on a fl upper arm. Hair at (not shaved) prior t DURAGESIC applica tion of the system, do oils, lotions, alcohol, the skin or alter its completely prior to s DURAGESIC should from the sealed packa any way prior to app

Body as a Whole: abdominal pain*, headache*
Cardiovascular: arrhythmia, chest pain
Digestive: nausea**, vomiting**, constipation**, dry mouth**, anorexia*, diarrhea*, dyspepsia*, flatulence
Nervous: somnolence**, confusion**, asthenia**, dizziness*, nervousness*, hallucinations*, anxiety*, depression*, euphoria*, tremor, abnormal coordination, speech disorder, abnormal thinking, abnormal gait, abnormal dreams, agitation, paresthesia, amnesia, syncope, paranoid reaction
Respiratory: dyspnea*, hypoventilation*, apnea*, hemoptysis, pharyngitis, hiccups
Skin and Appendages: sweating**, pruritus*, rash, application site reaction - erythema, papules, itching, edema
Urogenital: urinary retention*

*Reactions occurring in 3%–10% of DURAGESIC patients
**Reactions occurring in 10% or more of DURAGESIC patients

The following adverse effects have been reported in less than 1% of the 510 postoperative and cancer patients studied; the association between these events and DURAGESIC administration is unknown. This information is listed to serve as alerting information for the physician.
Digestive: abdominal distention
Nervous: aphasia, hypertonia, vertigo, stupor, hypotonia, depersonalization, hostility
Respiratory: stertorous breathing, asthma, respiratory disorder
Skin and Appendages, General: exfoliative dermatitis, pustules
Special Senses: amblyopia
Urogenital: bladder pain, oliguria, urinary frequency

DRUG ABUSE AND DEPENDENCE

Fentanyl is a Schedule II controlled substance and can produce drug dependence similar to that produced by morphine. DURAGESIC therefore has the potential for abuse. Tolerance, physical and psychological dependence may develop upon repeated administration of opioids. Iatrogenic addiction following opioid administration is relatively rare. Physicians should not let concerns of physical dependence deter them from using adequate amounts of opioids in the management of severe pain when such use is indicated.

OVERDOSAGE

Clinical Presentation

The manifestations of fentanyl overdosage are an extension of its pharmacologic actions with the most serious significant effect being hypoventilation.

Treatment

For the management of hypoventilation immediate countermeasures include removing the DURAGESIC system and physically or verbally stimulating the patient. These actions can be followed by administration of a specific narcotic antagonist such as naloxone. The duration of hypoventilation following an overdose may be longer than the effects of the narcotic antagonist's action (the half-life of naloxone ranges from 30 to 81 minutes). The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after system removal; repeated administration of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and the release of catecholamines.

If the clinical situation warrants, ensure a patent airway is established and maintained, administer oxygen and assist or control respiration as indicated and use an oropharyngeal airway or endotracheal tube if necessary. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy.

DOSAGE AND ADMINISTRATION

With all opioids, the safety of patients using the products is dependent on health care practitioners prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

As with all opioids, dosage should be individualized. The most important factor to be considered in determining the appropriate dose is the extent of preexisting opioid tolerance. (See BOX WARNING and CONTRAINDICATIONS.) Initial doses should be reduced in elderly or debilitated patients (see PRECAUTIONS).

DURAGESIC should be applied to non-irritated and non-irradiated skin on a flat surface such as chest, back, flank or upper arm. Hair at the application site should be clipped (not shaved) prior to system application. If the site of DURAGESIC application must be cleansed prior to application of the system, do so with clear water. Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics. Allow the skin to dry completely prior to system application.

DURAGESIC should be applied immediately upon removal from the sealed package. Do not alter the system, e.g., cut, in any way prior to application.

The transdermal system should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges.

Each DURAGESIC may be worn continuously for 72 hours. If analgesia for more than 72 hours is required, a new system should be applied to a different skin site after removal of the previous transdermal system.

DURAGESIC should be kept out of the reach of children. Used systems should be folded so that the adhesive side of the system adheres to itself, then the system should be flushed down the toilet immediately upon removal. Patients should dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused systems should be removed from their pouch and flushed down the toilet.

Dose Selection

DOSES MUST BE INDIVIDUALIZED BASED UPON THE STATUS OF EACH PATIENT AND SHOULD BE ASSESSED AT REGULAR INTERVALS AFTER DURAGESIC APPLICATION. REDUCED DOSES OF DURAGESIC ARE SUGGESTED FOR THE ELDERLY AND OTHER GROUPS DISCUSSED IN PRECAUTIONS.

DURAGESIC DOSES GREATER THAN 25 μG/H SHOULD NOT BE USED FOR INITIATION OF DURAGESIC THERAPY IN NON-OPIOID TOLERANT PATIENTS.

In selecting an initial DURAGESIC dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (eg whether it is a pure agonist or mixed agonist-antagonist), 2) the reliability of the relative potency estimates used to calculate the DURAGESIC dose needed (potency estimates may vary with the route of administration), 3) the degree of opioid tolerance, if any, and 4) the general condition and medical status of the patient. Each patient should be maintained at the lowest dose providing acceptable pain control.

Initial DURAGESIC Dose Selection

There has been no systematic evaluation of DURAGESIC as an initial opioid analgesic in the management of chronic pain, since most patients in the clinical trials were converted to DURAGESIC from other narcotics. Therefore, unless the patient has pre-existing opioid tolerance, the lowest DURAGESIC dose, 25 μg/h, should be used as the initial dose.

To convert patients from oral or parenteral opioids to DURAGESIC use the following methodology:

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using Table B.
3. Table C displays the range of 24-hour oral morphine doses that are recommended for conversion to each DURAGESIC dose. Use this table to find the calculated 24-hour morphine dose and the corresponding DURAGESIC dose. Initiate DURAGESIC treatment using the recommended dose and titrate patients upwards (no more frequently than every 3 days after the initial dose or than every 6 days thereafter) until analgesic efficacy is attained. For delivery rates in excess of 100 μg/h, multiple systems may be used.

TABLE B
EQUIANALGESIC POTENCY CONVERSION

Name	Equianalgesic Dose (mg) IM[a]	PO
morphine	10	60 (30)[b]
hydromorphone (Dilaudid®)	1.5	7.5
methadone (Dolophine®)	10	20
oxycodone (Percocet®)	15	30
levorphanol (Levo-Dromoran®)	2	4
oxymorphone (Numorphan®)	1	10 (PR)
heroin	5	60
meperidine (Demerol®)	75	—
codeine	130	200

Note: All IM and PO doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect. IM denotes intramuscular, PO oral, and PR rectal.

[a] Based on single-dose studies in which an intramuscular dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from parenteral to an oral route.

[b] The conversion ratio of 10 mg parenteral morphine = 30 mg oral morphine is based on clinical experience in patients with chronic pain.

Reference:

[a] Foley, K.M. (1985) The treatment of cancer pain. NEJM 313(2):84-95.

[b] Ashburn and Lipman (1993) Management of pain in the cancer patient. Anesth Analg 76: 402–416.

TABLE C
RECOMMENDED DURAGESIC DOSE BASED UPON DAILY ORAL MORPHINE DOSE

Oral 24-hour Morphine (mg/day)	DURAGESIC Dose (μg/hr)
45–134	25
135–224	50
225–314	75
315–404	100
405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1034	275
1035–1124	300

NOTE: In clinical trials these ranges of daily oral morphine doses were used as a basis for conversion to DURAGESIC. Although controlled studies are not available, in clinical practice it is customary to consider the doses of opioid given IM, IV or subcutaneously to be equivalent. There may be some differences in pharmacokinetic parameters such as C_{max} and T_{max}.

The majority of patients are adequately maintained with DURAGESIC administered every 72 hours. A small number of patients may not achieve adequate analgesia using this dosing interval and may require systems to be applied every 48 hours rather than every 72 hours. An increase in the DURAGESIC dose should be evaluated before changing dosing intervals in order to maintain patients on a 72-hour regimen.

Because of the increase in serum fentanyl concentration over the first 24 hours following initial system application, the initial evaluation of the maximum analgesic effect of DURAGESIC cannot be made before 24 hours of wearing. The initial DURAGESIC dosage may be increased after 3 days (see Dose Titration).

During the initial application of DURAGESIC, patients should use short-acting analgesics for the first 24 hours as needed until analgesic efficacy with DURAGESIC is attained. Thereafter, some patients still may require periodic supplemental doses of other short-acting analgesics for 'breakthrough' pain.

Dose Titration

The conversion ratio from oral morphine to DURAGESIC is conservative, and 50% of patients are likely to require a dose increase after initial application of DURAGESIC. The initial DURAGESIC dosage may be increased after 3 days, based on the daily dose of supplemental analgesics required by the patient in the second or third day of the initial application.

Physicians are advised that it may take up to 6 days after increasing the dose of DURAGESIC for the patient to reach equilibrium on the new dose (see graph in CLINICAL PHARMACOLOGY). Therefore, patients should wear a higher dose through two applications before any further increase in dosage is made on the basis of the average daily use of a supplemental analgesic.

Appropriate dosage increments should be based on the daily dose of supplementary opioids, using the ratio of 90 mg/24 hours of oral morphine to a 25 μg/h increase in DURAGESIC dose.

Discontinuation of DURAGESIC

To convert patients to another opioid, remove DURAGESIC and titrate the dose of the new analgesic based upon the patient's report of pain until adequate analgesia has been attained. Upon system removal, 17 hours or more are required for a 50% decrease in serum fentanyl concentrations. For patients requiring discontinuation of opioids, a gradual downward titration is recommended since it is not known what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

HOW SUPPLIED

DURAGESIC® is supplied in cartons containing 5 individually packaged systems. See chart for information regarding individual systems.

DURAGESIC Dose (μg/h)	System Size (cm^2)	Fentanyl Content (mg)	NDC Number
DURAGESIC®-25	10	2.5	50458-033-05
DURAGESIC®-50*	20	5	50458-034-05
DURAGESIC®-75*	30	7.5	50458-035-05
DURAGESIC®-100*	40	10	50458-036-05

*FOR USE ONLY IN OPIOID TOLERANT PATIENTS.

Safety and Handling

DURAGESIC is supplied in sealed transdermal systems which pose little risk of exposure to health care workers. If the gel from the drug reservoir accidentally contacts the

Continued on next page

Janssen Pharmaceutica—Cont.

skin, the area should be washed with copious amounts of water. Do not use soap, alcohol, or other solvents to remove the gel because they may enhance the drug's ability to penetrate the skin. Do not cut or damage DURAGESIC. If the DURAGESIC system is cut or damaged, controlled drug delivery will not be possible.
Do not store above 77°F (25°C). Apply immediately after removal from individual sealed package. Do not use if the seal is broken. **For transdermal use only.**
CAUTION: Federal law prohibits dispensing without prescription
DEA order form required. A schedule CII narcotic.
Manufactured by:
ALZA Corporation
Palo Alto, CA 94304
Distributed by:
JANSSEN PHARMACEUTICA
Titusville, NJ 08560
January 1994 June 1994 7500309
Shown in Product Identification Guide, page 318

ERGAMISOL® ℞
[*ər-gam'ə-, sōl*]
(levamisole hydrochlorid)
Tablets

DESCRIPTION

ERGAMISOL (levamisole hydrochloride) is an immunomodulator available in tablets for oral administration containing the equivalent of 50 mg as levamisole base. Fifty-nine (59) mg of levamisole HCl is equivalent to 50 mg of levamisole base. Inactive ingredients are colloidal silicon dioxide, hydrogenated vegetable oil, hydroxypropyl methylcellulose, lactose, microcrystalline cellulose, polyethylene glycol 6000, polysorbate 80, and talc.
Levamisole hydrochloride is (-)-(S)-2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole monohydrochloride.
Levamisole hydrochloride is a white to pale cream colored crystalline powder which is almost odorless and is freely soluble in water. It is quite stable in acid aqueous media but hydrolyzes in alkaline or neutral solutions. It has a molecular weight of 240.75.

CLINICAL PHARMACOLOGY

Two clinical trials having essentially the same design have demonstrated an increase in survival and a reduction in recurrence rate in the subset of patients with resected Dukes' C colon cancer treated with a regimen of ERGAMISOL (levamisole hydrochloride) plus fluorouracil[1,2]. After surgery, patients were randomized to no further therapy, ERGAMISOL alone, or ERGAMISOL plus fluorouracil.
In one clinical trial in which 408 Dukes' B and C colorectal cancer patients were studied, 262 Dukes' C patients were evaluated for a minimum follow-up of five years[1]. A subset analysis of these Dukes' C patients showed the estimated reduction in death rate was 27% for ERGAMISOL plus fluorouracil ($p = 0.11$) and 28% for ERGAMISOL alone ($p = 0.11$)[3]. The estimated reduction in recurrence rate was 36% for ERGAMISOL plus fluorouracil ($p = 0.025$) and 28% for ERGAMISOL alone ($p = 0.11$)[3]. In another clinical trial designed to confirm the above results, 929 Dukes' C colon cancer patients were evaluated for a minimum follow-up of 2 years[2]. The estimated reduction in death rate was 33% for ERGAMISOL plus fluorouracil ($p = 0.006$). The estimated reduction in recurrence rate was 41% for ERGAMISOL plus fluorouracil ($p < 0.0001$). The ERGAMISOL alone group did not show advantage over no treatment on improving recurrence or survival rates. There are presently insufficient data to evaluate the effect of the combination of ERGAMISOL plus fluorouracil in Dukes' B patients. There are also insufficient data to evaluate the effect of ERGAMISOL plus fluorouracil in patients with rectal cancer because only 12 patients with rectal cancer were treated with the combination in the first study and none in the second study.
The mechanism of action of ERGAMISOL in combination with fluorouracil is unknown. The effects of levamisole on the immune system are complex. The drug appears to restore depressed immune function rather than to stimulate response to above-normal levels. Levamisole can stimulate formation of antibodies to various antigens, enhance T-cell responses by stimulating T-cell activation and proliferation, potentiate monocyte and macrophage functions including phagocytosis and chemotaxis, and increase neutrophil mobility, adherence, and chemotaxis. Other drugs have similar short-term effects and the clinical relevance is unclear.
Besides its immunomodulatory function, levamisole has other mammalian pharmacologic activities, including inhibition of alkaline phosphatase, and cholinergic activity.
The pharmacokinetics of ERGAMISOL have not been studied in the dosage regimen recommended with fluorouracil nor in patients with hepatic insufficiency. After administration of a single oral dose of 50 mg of a research formulation of ERGAMISOL, it appears that levamisole is rapidly absorbed from the gastrointestinal tract. Mean peak plasma concentrations of 0.13 mcg/ml are attained within 1.5 to 2 hours. The plasma elimination half-life of levamisole is between 3-4 hours. Following a 150-mg radio-labelled dose, levamisole is extensively metabolized by the liver in humans and the metabolities excreted mainly by the kidneys (70% over 3 days). The elimination half-life of metabolite excretion is 16 hours. Approximately 5% is excreted in the feces. Less than 5% is excreted unchanged in the urine and less than 0.2% in the feces. Approximately 12% is recovered in the urine as the glucuronide of p-hydroxy-levamisole. The clinical significance of these data are unknown since a 150-mg dose may not be proportional to a 50-mg dose.

INDICATIONS AND USAGE

ERGAMISOL (levamisole hydrochloride) is only indicated as adjuvant treatment in combination with fluorouracil after surgical resection in patients with Dukes' stage C colon cancer.

CONTRAINDICATIONS

ERGAMISOL (levamisole hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug or its components.

WARNINGS

ERGAMISOL (levamisole hydrochloride) has been associated with agranulocytosis, sometimes fatal. The onset of agranulocytosis is frequently accompanied by a flu-like syndrome (fever, chills, etc.); however, in a small number of patients it is asymptomatic. A flu-like syndrome may also occur in the absence of agranulocytosis. It is essential that appropriate hematological monitoring be done routinely during therapy with ERGAMISOL and fluorouracil. Neutropenia is usually reversible following discontinuation of therapy. Patients should be instructed to report immediately any flu-like symptoms.
Higher than recommended doses of ERGAMISOL may be associated with an increased incidence of agranulocytosis, so the recommended dose should not be exceeded.
The combination of ERGAMISOL and fluorouracil has been associated with frequent neutropenia, anemia and thrombocytopenia.

PRECAUTIONS

Before beginning this combination adjuvant treatment, the physician should become familiar with the labeling for fluorouracil.
Information for Patients: The patient should be informed that if flu-like symptoms or malaise occurs, the physician should be notified immediately.
Drug Interactions: ERGAMISOL (levamisole hydrochloride) has been reported to produce "ANTABUSE®"-like side effects when given concomitantly with alcohol. Concomitant administration of phenytoin and ERGAMISOL plus fluorouracil has led to increased plasma levels of phenytoin. The physician is advised to monitor plasma levels of phenytoin and to decrease the dose if necessary.
Because of reports of prolongation of the prothrombin time beyond the therapeutic range in patients taking concurrent levamisole and warfarin sodium, it is suggested that the prothrombin time be monitored carefully, and the dose of warfarin sodium or other coumarin-like drugs should be adjusted accordingly, in patients taking both drugs.
Laboratory Tests: On the first day of therapy with ERGAMISOL/fluorouracil, patients should have a CBC with differential and platelets, electrolytes and liver function tests performed. Thereafter, a CBC with differential and platelets should be performed weekly prior to each treatment with fluorouracil with electrolytes and liver function tests peformed every 3 months for a total of one year. Dosage modifications should be instituted as follows: If WBC is 2500-3500/mm^3 defer the fluorouracil dose until WBC is > 3500/mm^3. If WBC is < 2500/mm^3, defer the fluorouracil dose until WBC is > 3500/mm^3; then resume the fluorouracil dose reduced by 20%. If WBC remains < 2500/mm^3 for over 10 days despite deferring fluorouracil, discontinue administration of ERGAMISOL. Both drugs should be deferred unless enough platelets are present (≥ 100,000/mm^3).
Carcinogensis, Mutagenesis, Impairment of Fertility: Adequate animal carcinogenicity studies have not been conducted with levamisole. Studies of levamisole administered in drinking water at 5, 20, and 80 mg/kg/day to mice for up to 18 months or adminstered to rats in the diet at 5, 20, and 80 mg/kg/day for 24 months showed no evidence of neoplastic effects. These studies were not conducted at the maximum tolerated dose, therefore the animals may not have been exposed to a reasonable drug challenge. No mutagenic effects were demonstrated in dominant lethal studies in male and female mice, in an Ames test, and in a study to detect chromosomal aberrations in cultured peripheral human lymphocytes.
Adverse effects were not observed on male or female fertility when levamisole was administered to rats in the diet at doses of 2.5, 10, 40, and 160 mg/kg. In a rat gavage study at doses of 20, 60, and 180 mg/kg, the copulation period was increased, the duration of pregnancy was slightly increased, and fertility, pup viability and weight, lactation index, and number of fetuses were decreased at 60 mg/kg. No negative reproductive effects were present when the offspring were allowed to mate and litter.
Pregnancy: Pregnancy Category C: Teratogenicity studies have been performed in rats and rabbits at oral doses up to 180 mg/kg. Fetal malformations were not observed. In rats, embryotoxicity was present at 160 mg/kg and in rabbits, significant embryotoxicity was observed at 180 mg/kg. There are no adequate and well-controlled studies in pregnant women and ERGAMISOL should not be administered unless the potential benefits outweigh the risks. Women taking the combination of ERGAMISOL and fluorouracil should be advised not to become pregnant.
Nursing Mothers: It is not known whether ERGAMISOL is excreted in human milk; it is excreted in cows' milk. Because of the potential for serious adverse reactions in nursing infants from ERGAMISOL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness of ERGAMISOL in children have not been established.

ADVERSE REACTIONS

Almost all patients receiving ERGAMISOL (levamisole hydrochloride) and fluorouracil reported adverse experiences. Tabulated below is the incidence of adverse experiences that occurred in at least 1% of patients enrolled in two clinical trials who were adjuvantly treated with either ERGAMISOL or ERGAMISOL plus fluorouracil following colon surgery. In the larger clinical trial, 66 of 463 patients (14%) discontinued the combination of ERGAMISOL plus fluorouracil because of adverse reactions. Forty-three of these patients (9%) developed isolated or a combination of gastrointestinal toxicities. (e.g., nausea, vomiting, diarrhea, stomatitis and anorexia). Ten patients developed rash and/or pruritus. Five patients discontinued therapy because of flu-like symptoms or fever with chills; ten patients developed central nervous system symptoms such as dizziness, ataxia, depression, confusion, memory loss, weakness, inability to concentrate, and headache; two patients developed reversible neutropenia and sepsis; one patient because of thrombocytopenia; one patient because of hyperbilirubinemia. One patient in the ERGAMISOL plus fluorouracil group developed agranulocytosis and sepsis and died.
In the ERGAMISOL alone arm of the trial, 15 of 310 patients (4.8%) discontinued therapy because of adverse experiences. Six of these (2%) discontinued because of rash, six because of arthralgia/myalgia, and one each for fever and neutropenia, urinary infection, and cough.
[See table at top of next page.]

In worldwide experience with ERGAMISOL, less frequent adverse experiences included exfoliative dermatitis, fixed drug eruptions, periorbital edema, vaginal bleeding, anaphylaxis, confusion, convulsions, hallucinations, impaired concentration, renal failure, pancreatitis, elevated serum creatinine, and increased alkaline phosphatase.
Reports of hyperlipidema have been observed in patients receiving combination therapy of ERGAMISOL and fluorouracil; elevations in triglyceride levels have been greater than increases in cholesterol levels. In worldwide postmarketing experience with the combination therapy, there have been rare cases of elevated hepatic enzymes and hepatosteatosis in patients.
Cases of an encephalopathy—like syndrome associated with demyelination have been reported in patients treated with ERGAMISOL. Worldwide postmarketing experience with the combination therapy of ERGAMISOL and fluorouracil has also included reports of peripheral neuropathy and multifocal inflammatory leukoencephalopathy. The onset of symptoms and the clinical presentation in these cases are quite varied. Symptoms may include coma, confusion, lethargy, memory loss, muscle weakness, parathesia, and speech disturbances. This condition has been associated with MRI and CT scan findings of demyelinating lesions in the white matter. If an acute neurological syndrome occurs, immediate discontinuation of ERGAMISOL and fluorouracil therapy should be discontinued immediately. Patients have generally recovered/improved with drug discontinuation and corticosteroid therapy.
The following additional adverse experiences have been reported for fluorouracil alone: esophagopharyngitis, pancytopenia, myocardial ischemia, angina, gastrointestinal ulceration and bleeding, anaphylaxis and generalized allergic reactions, acute cerebellar syndrome, nystagmus, dry skin, fissuring, photosensitivity, lacrimal duct stenosis, photophobia, euphoria, thrombophlebitis, and nail changes.

OVERDOSAGE

Fatalities have been reported in a three-year-old child who ingested 15 mg/kg and in an adult who ingested 32 mg/kg. No further clinical information is available. In cases of overdosage, gastric lavage and supportiv

Adverse experience

Gastrointestinal
Nausea
Diarrhea
Stomatitis
Vomiting
Anorexia
Abdominal pain
Constipation
Flatulence
Dyspepsia
Hematological
Leukopenia
< 2000/mm^3
≥ 2000 to < 4000/r
≥ 4000/mm^3
unscored category
Thrombocytopenia
< 50,000/mm^3
≥ 50,000 to < 130,(
≥ 130,000/mm^3
Anemia
Granulocytopenia
Epistaxis
Skin and Appendage
Dermatitis
Alopecia
Pruritus
Skin discoloration
Urticaria
Body as a Whole
Fatigue
Fever
Rigors
Chest pain
Edema
Resistance Mechanis
Infection
Special Senses
Taste Perversion
Altered sense of smel
Musculoskeletal Syst
Arthralgia
Myalgia
Central and periphera
Dizziness
Headache
Paresthesia
Ataxia
Psychiatric
Somnolence
Depression
Nervousness
Insomnia
Anxiety
Forgetfulness
Vision
Abnormal tearing
Blurred vision
Conjunctivitis
Liver and biliary syste
Hyperbilirubinemia

DOSAGE AND ADM

The adjuvant use of ride) and fluorouracil schedule:
Initial Therapy:
ERGAMISOL: 50 mg q8h for 3 days
fluorouracil: 450 mg/n IV for 5 days concomitant with a of ERGAMISOL
Maintenance:
ERGAMISOL: 50 mg fluorouracil: 450 mg/ 28 days after the initi
Treatment: ERGAMI initiated no earlier th surgery at a dose of 50 days for 1 year. Fluoro earlier than 21 days an providing the patient maintaining normal or and is fully recovered fi

with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be given as a liquid preparation or as an aqueous (water) suspension of K-DUR (see **PRECAUTIONS; Information for Patients,** and **DOSAGE AND ADMINISTRATION** sections).

All solid oral dosage forms of potassium chloride are contraindicated in any patient in whom there is structural, pathological (e.g., diabetic gastroparesis) or pharmacologic (use of anticholinergic agents or other agents with anticholinergic properties at sufficient doses to exert anticholinergic effects) cause for arrest or delay in tablet passage through the gastrointestinal tract.

WARNINGS

Hyperkalemia (see **OVERDOSAGE**)—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone, triamterene or amiloride) since the simultaneous administration of these agents can produce severe hyperkalemia.

Interaction with Angiotensin Converting Enzyme Inhibitors—Angiotensin converting enzyme (ACE) inhibitors (e.g., captopril, enalapril) will produce some potassium retention by inhibiting aldosterone production. Potassium supplements should be given to patients receiving ACE inhibitors only with close monitoring.

Gastrointestinal Lesions—Solid oral dosage forms of potassium chloride can produce ulcerative and/or stenotic lesions of the gastrointestinal tract. Based on spontaneous adverse reaction reports, enteric coated preparations of potassium chloride are associated with an increased frequency of small bowel lesions (40–50 per 100,000 patient years) compared to sustained release wax matrix formulations (less than one per 100,000 patient years). Because of the lack of extensive marketing experience with microencapsulated products, a comparison between such products and wax matrix or enteric coated products is not available. K-DUR is a tablet formulated to provide a controlled rate of release of microencapsulated potassium chloride and thus to minimize the possibility of a high local concentration of potassium near the gastrointestinal wall.

Prospective trials have been conducted in normal human volunteers in which the upper gastrointestinal tract was evaluated by endoscopic inspection before and after one week of solid oral potassium chloride therapy. The ability of this model to predict events occurring in usual clinical practice is unknown. Trials which approximated usual clinical practice did not reveal any clear differences between the wax matrix and microencapsulated dosage forms. In contrast, there was a higher incidence of gastric and duodenal lesions in subjects receiving a high dose of a wax matrix controlled release formulation under conditions which did not resemble usual or recommended clinical practice (i.e., 96 mEq per day in divided doses of potassium chloride administered to fasted patients, in the presence of an anticholinergic drug to delay gastric emptying). The upper gastrointestinal lesions observed by endoscopy were asymptomatic and were not accompanied by evidence of bleeding (Hemoccult testing). The relevance of these findings to the usual conditions (i.e., nonfasting, no anticholinergic agent, smaller doses) under which controlled release potassium chloride products are used is uncertain; epidemiologic studies have not identified an elevated risk, compared to microencapsulated products, for upper gastrointestinal lesions in patients receiving wax matrix formulations. K-DUR should be discontinued immediately and the possibility of ulceration, obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS

General: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Information for Patients: Physicians should consider reminding the patient of the following:

To take each dose with meals and with a full glass of water or other liquid.

To take each dose without crushing, chewing, or sucking the tablets. If those patients are having difficulty swallowing whole tablets, they may try one of the following alternate methods of administration:

a. Break the tablet in half, and take each half separately with a glass of water.
b. Prepare an aqueous (water) suspension as follows:
   1. Place the whole tablet(s) in approximately one-half glass of water (4 fluid ounces).
   2. Allow approximately 2 minutes for the tablet(s) to disintegrate.
   3. Stir for about half a minute after the tablet(s) has disintegrated.
   4. Swirl the suspension and consume the entire contents of the glass immediately by drinking or by the use of a straw.
   5. Add another one fluid ounce of water, swirl, and consume immediately.
   6. Then, add an additional one fluid ounce of water, swirl, and consume immediately.

Aqueous suspension of K-DUR tablets that is not taken immediately should be discarded. The use of other liquids for suspending K-DUR tablets is not recommended.

To take this medicine following the frequency and amount prescribed by the physician. This is especially important if the patient is also taking diuretics and/or digitalis preparations.

To check with the physician at once if tarry stools or other evidence of gastrointestional bleeding is noticed.

Laboratory Tests: When blood is drawn for analysis of plasma potassium it is important to recognize that artifactual elevations can occur after improper venipuncture technique or as a result of in-vitro hemolysis of the sample.

Drug Interactions: Potassium-sparing diuretics, angiotensin converting enzyme inhibitors (see **WARNINGS**).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity and fertility studies in animals have not been performed. Potassium is a normal dietary constituent.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is unlikely that potassium supplementation that does not lead to hyperkalemia would have an adverse effect on the fetus or would affect reproductive capacity.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**).

The most common adverse reactions to oral potassium salts are nausea, vomiting, flatulence, abdominal pain/discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals or reducing the amount taken at one time.

OVERDOSAGE

The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration (6.5–8.0 mEq/L) and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest. (9–12 mEq/L).

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of any agents with potassium-sparing properties.
2. Intravenous administration of 300 to 500 mL/hr of 10% dextrose solution containing 10–20 units of crystalline insulin per 1,000 mL.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

DOSAGE AND ADMINISTRATION

The usual dietary intake of potassium by the average adult is 50 to 100 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient. The dose for the prevention of hypokalemia is typically in the range of 20 mEq per day. Doses of 40–100 mEq per day or more are used for the treatment of potassium depletion. Dosage should be divided if more than 20 mEq per day is given such that no more than 20 mEq is given in a single dose.

Each K-DUR 20 tablet provides 20 mEq of potassium chloride.

Each K-DUR 10 tablet provides 10 mEq of potassium chloride.

K-DUR tablets should be taken with meals and with a glass of water or other liquid. This product should not be taken on an empty stomach because of its potential for gastric irritation (see **WARNINGS**).

Patients having difficulty swallowing whole tablets may try one of the following alternate methods of administration:

a. Break the tablet in half, and take each half separately with a glass of water.
b. Prepare an aqueous (water) suspension as follows:
   1. Place the whole tablet(s) in approximately one-half glass of water (4 fluid ounces).
   2. Allow approximately 2 minutes for the tablet(s) to disintegrate.
   3. Stir for about half a minute after the tablet(s) has disintegrated.
   4. Swirl the suspension and consume the entire contents of the glass immediately by drinking or by the use of a straw.
   5. Add another one fluid ounce of water, swirl, and consume immediately.
   6. Then, add an additional one fluid ounce of water, swirl, and consume immediately.

Aqueous suspension of K-DUR tablets that is not taken immediately should be discarded. The use of other liquids for suspending K-DUR tablets is not recommended.

HOW SUPPLIED

K-DUR 20 mEq Extended Release Tablets are available in bottles of 100 (NDC 0085-0787-01); bottles of 500 (NDC 0085-0787-06); bottles of 1000 (NDC 0085-0787-10) and boxes of 100 for unit dose dispensing (NDC 0085-0787-81). K-DUR 20 mEq tablets are white, oblong, imprinted K-DUR 20 and scored for flexibility of dosing.

K-DUR 10 mEq Extended Release Tablets are available in bottles of 100 (NDC 0085-0263-01) and boxes of 100 for unit dose dispensing (NDC 0085-0263-81). K-DUR 10 mEq tablets are white, oblong, imprinted K-DUR 10.

STORAGE CONDITIONS

Keep tightly closed. Store at controlled room temperature 15–30°C (59–86°F).

CAUTION

Federal law prohibits dispensing without prescription.

Rev. 4/90 14274766

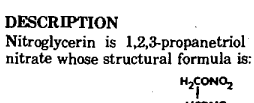
Shown in Product Identification Guide, page 319

NITRO-DUR® R

(nitroglycerin)
Transdermal Infusion System

DESCRIPTION

Nitroglycerin is 1,2,3-propanetriol trinitrate, an organic nitrate whose structural formula is:



and whose molecular weight is 227.09. The organic nitrates are vasodilators, active on both arteries and veins.

The NITRO-DUR (nitroglycerin) Transdermal Infusion System is a flat unit designed to provide continuous controlled release of nitroglycerin through intact skin. The rate of release of nitroglycerin is linearly dependent upon the area of the applied system; each cm^2 of applied system delivers ap-

Continued on next page

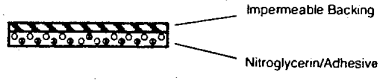
Key—Cont.

proximately 0.02 mg of nitroglycerin per hour. Thus, the 5-, 10-, 15-, 20-, 30-, and 40-cm^2 systems deliver approximately 0.1, 0.2, 0.3, 0.4, 0.6, and 0.8 mg of nitroglycerin per hour, respectively.

The remainder of the nitroglycerin in each system serves as a reservoir and is not delivered in normal use. After 12 hours, for example, each system has delivered approximately 6% of its original content of nitroglycerin.

The NITRO-DUR transdermal system contains nitroglycerin in acrylic-based polymer adhesives with a resinous cross-linking agent to provide a continuous source of active ingredient. Each unit is sealed in a paper polyethylene-foil pouch.

Cross section of the system.



CLINICAL PHARMACOLOGY

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.

Pharmacokinetics: The volume of distribution of nitroglycerin is about 3 L/kg, and nitroglycerin is cleared from this volume at extremely rapid rates, with a resulting serum half-life of about 3 minutes. The observed clearance rates (close to 1 L/kg/min) greatly exceed hepatic blood flow; known sites of extrahepatic metabolism include red blood cells and vascular walls.

The first products in the metabolism of nitroglycerin are inorganic nitrate and the 1,2- and 1,3-dinitroglycerols. The dinitrates are less effective vasodilators than nitroglycerin, but they are longer-lived in the serum, and their net contribution to the overall effect of chronic nitroglycerin regimens is not known. The dinitrates are further metabolized to (non-vasoactive) mononitrates and, ultimately, to glycerol and carbon dioxide.

To avoid development of tolerance to nitroglycerin, drug-free intervals of 10–12 hours are known to be sufficient; shorter intervals have not been well studied. In one well-controlled clinical trial, subjects receiving nitroglycerin appeared to exhibit a rebound or withdrawal effect, so that their exercise tolerance at the end of the daily drug-free interval was *less* than that exhibited by the parallel group receiving placebo.

In healthy volunteers, steady-state plasma concentrations of nitroglycerin are reached by about 2 hours after application of a patch and are maintained for the duration of wearing the system (observations have been limited to 24 hours). Upon removal of the patch, the plasma concentration declines with a half-life of about an hour.

Clinical Trials: Regimens in which nitroglycerin patches were worn for 12 hours daily have been studied in well-controlled trials up to 4 weeks in duration. Starting about 2 hours after application and continuing until 10–12 hours after application, patches that deliver at least 0.4 mg of nitroglycerin per hour have consistently demonstrated greater antianginal activity than placebo. Lower-dose patches have not been as well studied, but in one large, well-controlled trial in which higher-dose patches were also studied, patches delivering 0.2 mg/hr had significantly *less* antianginal activity than placebo.

It is reasonable to believe that the rate of nitroglycerin absorption from patches may vary with the site of application, but this relationship has not been adequately studied.

INDICATIONS AND USAGE

Transdermal nitroglycerin is indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute attack.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

WARNINGS

The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a NITRO-DUR patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS

General: Severe hypotension, particularly with upright posture, may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to other forms of nitroglycerin develops, the effects of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10- to 12-hour, nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients had decreased exercise tolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is unknown.

Information for Patients: Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets.

A patient leaflet is supplied with the systems.

Drug Interactions: The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Animal carcinogenesis studies with topically applied nitroglycerin have not been performed.

Rats receiving up to 434 mg/kg/day of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes. At high dose, the incidences of hepatocellular carcinomas in both sexes were 52% vs. 0% in controls, and incidences of testicular tumors were 52% vs. 8% in controls. Lifetime dietary administration of up to 1058 mg/kg/day of nitroglycerin was not tumorigenic in mice.

Nitroglycerin was weakly mutagenic in Ames tests performed in two different laboratories. Nevertheless, there was no evidence of mutagenicity in an *in vivo* dominant lethal assay with male rats treated with doses up to about 363 mg/kg/day, p.o., or in *in vitro* cytogenetic tests in rat and dog tissues.

In a three-generation reproduction study, rats received dietary nitroglycerin at doses up to about 434 mg/kg/day for 6 months prior to mating of the F_0 generation with treatment continuing through successive F_1 and F_2 generations. The high dose was associated with decreased feed intake and body weight gain in both sexes at all matings. No specific effect on the fertility of the F_0 generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and aspermatogenesis in the high-dose males. In this three-generation study there was no clear evidence of teratogenicity.

Pregnancy: Pregnancy Category C:

Animal teratology studies have not been conducted with nitroglycerin transdermal systems. Teratology studies in rats and rabbits, however, were conducted with topically applied nitroglycerin ointment at doses up to 80 mg/kg/day and 240 mg/kg/day, respectively. No toxic effects on dams or fetuses were seen at any dose tested. There are no adequate and well-controlled studies in pregnant women. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to nitroglycerin are generally dose related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Allergic reactions to nitroglycerin are also uncommon, and the great majority of those reported have been cases of contact dermatitis or fixed drug eruptions in patients receiving nitroglycerin in ointments or patches. There have been few reports of genuine anaphylactoid reactions, and these reactions can probably occur in patients receiving nitroglycerin by any route.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see OVERDOSAGE).

Application-site irritation may occur but is rarely severe.

In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

	Placebo	Patch
Headache	18%	63%
Lightheadedness	4%	6%
Hypotension, and/or Syncope	0%	4%
Increased Angina	2%	2%

OVERDOSAGE

Hemodynamic Effects: The ill effects of nitroglycerin overdose are generally the results of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (eg, maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which—if any—of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

NITRO-DUR Sy
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*In Vivo**

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NITRO-DUR System Rated Release *In Vivo**	Total Nitroglycerin Content	System Size	Package Size
0.1 mg/hr	20 mg	5 cm^2	Unit Dose 30 (NDC 0085-3305-30) Hospital Unit Dose 100 (NDC 0085-3305-01) Institutional Package 30 (NDC 0085-3305-35)
0.2 mg/hr	40 mg	10 cm^2	Unit Dose 30 (NDC 0085-3310-30) Hospital Unit Dose 100 (NDC 0085-3310-01) Institutional Package 30 (NDC 0085-3310-35)
0.3 mg/hr	60 mg	15 cm^2	Unit Dose 30 (NDC 0085-3315-30) Hospital Unit Dose 100 (NDC 0085-3315-01) Institutional Package 30 (NDC 0085-3315-35)
0.4 mg/hr	80 mg	20 cm^2	Unit Dose 30 (NDC 0085-3320-30) Hospital Unit Dose 100 (NDC 0085-3320-01) Institutional Package 30 (NDC 0085-3320-35)
0.6 mg/hr	120 mg	30 cm^2	Unit Dose 30 (NDC 0085-3330-30) Hospital Unit Dose 100 (NDC 0085-3330-01) Institutional Package 30 (NDC 0085-3330-35)
0.8 mg/hr	160 mg	40 cm^2	Unit Dose 30 (NDC 0085-0819-30) Hospital Unit Dose 100 (NDC 0085-0819-01) Institutional Package 30 (NDC 0085-0819-35)

*Release rates were formerly described in terms of drug delivered per 24 hours. In these terms, the supplied NITRO-DUR systems would be rated at 2.5 mg/24 hours (0.1 mg/hour), 5 mg/24 hours (0.2 mg/hour), 7.5 mg/24 hours (0.3 mg/hour), 10 mg/24 hours (0.4 mg/hour), and 15 mg/24 hours (0.6 mg/hour).

Methemoglobinemia: Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2–4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial PO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1–2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

The suggested starting dose is between 0.2 mg/hr* and 0.4 mg/hr*. Doses between 0.4 mg/hr* and 0.8 mg/hr* have shown continued effectiveness for 10–12 hours daily for at least 1 month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10–12 hours is sufficient (see **CLINICAL PHARMACOLOGY**). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12–14 hours and a daily patch-off period of 10–12 hours.

*Release rates were formerly described in terms of drug delivered per 24 hours. In these terms, the supplied NITRO-DUR systems would be rated at 2.5 mg/24 hours (0.1 mg/hour), 5 mg/24 hours (0.2 mg/hour), 7.5 mg/24 hours (0.3 mg/hour), 10 mg/24 hours (0.4 mg/hour), and 15 mg/24 hours (0.6 mg/hour).

Although some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (ie, complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

HOW SUPPLIED

[See table above.]

Store between 15° and 30°C (59° and 86°F). Do not refrigerate.

CAUTION: Federal law prohibits dispensing without prescription.

Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA
Rev. 7/95 18143615

U. S. Patent No. 5,186,938
Shown in Product Identification Guide, page 319

THEO-DUR®

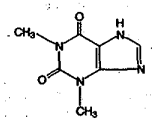
(theophylline)
Extended-Release Tablets

℞

DESCRIPTION

THEO-DUR® Extended-Release Tablets contain anhydrous theophylline in an extended-release formulation for oral administration which allows a 12-hour dosing interval for a majority of patients and a 24-hour dosing interval for selected patients (see **DOSAGE AND ADMINISTRATION** for a description of appropriate patient populations).

Theophylline:
Theophylline is a bronchodilator, structurally classified as a methylxanthine. It occurs as a white, odorless, crystalline powder with a bitter taste. Anhydrous theophylline has the chemical name 1*H*-Purine-2,6-dione,3,7-dihydro-1,3-dimethyl-, and is represented by the following structural formula:



The molecular formula of anhydrous theophylline is $C_7H_8N_4O_2$ with a molecular weight of 180.17.

THEO-DUR Extended-Release Tablets contain no color additives and are available in four strengths: 100 mg, 200 mg, 300 mg, and 450 mg.

The inactive ingredients for THEO-DUR 100 mg Extended-Release Tablets include: Acacia NF, Acetone USP, Alcohol, Cellulose Acetate Phthalate NF, Cetyl Alcohol NF, Chloroform NF, Confectioner's Sugar 6X NF, Corn Starch NF, Diethyl Phthalate (Ethyl Phthalate), Ethyl Acetate NF, Glyceryl Monostearate NF (Atmul 84), Isopropyl Alcohol USP, Lactose Monohydrate USP, Magnesium Stearate NF, Myristyl Alcohol, Non-Pareil Seeds 18–20 Mesh, Purified Water USP, Sodium Lauryl Sulfate NF (Dupanol C), Talc USP, and White Wax NF.

The inactive ingredients for THEO-DUR 200 mg, 300 mg, and 450 mg Extended-Release Tablets include: Acetone USP, Cellulose Acetate Phthalate NF, Cetyl Alcohol NF, Diethyl Phthalate (Ethyl Phthalate), Glyceryl Monostearate NF (Atmul 84), Hydroxypropyl Methylcellulose 2910 USP (Methocel E-50), Isopropyl Alcohol USP, Anhydrous Lactose USP, Magnesium Stearate NF, Myristyl Alcohol, Non-Pareil Seeds 18–20 Mesh, Purified Water USP, and White Wax NF.

CLINICAL PHARMACOLOGY

Mechanism of Action:
Theophylline has two distinct actions in the airways of patients with reversible obstruction; smooth muscle relaxation (ie, bronchodilation) and suppression of the response of the airways to stimuli (ie, non-bronchodilator prophylactic effects). While the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilatation is mediated by the inhibition of two isozymes of phosphodiesterase (PDE III and, to a lesser extent, PDE IV) while non-bronchodilator prophylactic actions are probably mediated through one or more different molecular mechanisms that do not involve inhibition of PDE III or antagonism of adenosine receptors. Some of the adverse effects associated with theophylline appear to be mediated by inhibition of PDE III (eg, hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (eg, alterations in cerebral blood flow).

Theophylline increases the force of contraction of diaphragmatic muscles. This action appears to be due to enhancement of calcium uptake through an adenosine-mediated channel.

Serum Concentration-Effect Relationship:
Bronchodilation occurs over the serum theophylline concentration range of 5–20 mcg/mL. Clinically important improvement in symptom control has been found in most studies to require peak serum theophylline concentrations >10 mcg/mL, but patients with mild disease may benefit from lower concentrations. At serum theophylline concentrations >20 mcg/mL, both the frequency and severity of adverse reactions increase. In general, maintaining peak serum theophylline concentrations between 10 and 15 mcg/mL will achieve most of the drug's potential therapeutic benefit while minimizing the risk of serious adverse events.

Pharmacokinetics:
Overview Theophylline is rapidly and completely absorbed after oral administration in solution or immediate-release solid oral dosage form. Theophylline does not undergo any appreciable pre-systemic elimination, distributes freely into fat-free tissues, and is extensively metabolized in the liver. The pharmacokinetics of theophylline vary widely among similar patients and cannot be predicted by age, sex, body weight, or other demographic characteristics. In addition, certain concurrent illnesses and alterations in normal physiology (see **Table I**) and coadministration of other drugs (see **Table II**) can significantly alter the pharmacokinetic characteristics of theophylline. Within-subject variability in metabolism has also been reported in some studies, especially in acutely ill patients. It is, therefore, recommended that serum theophylline concentrations be measured frequently in acutely ill patients (eg, at 24–hr intervals) and periodically in patients receiving long-term therapy (eg, at 6–12 month intervals). More frequent measurements should be made in the presence of any condition that may significantly alter theophylline clearance (see **PRECAUTIONS, Laboratory Tests** and **DOSAGE AND ADMINISTRATION**).

[See table 1 at bottom of next page.]

Absorption Theophylline is rapidly and completely absorbed after oral administration in solution or immediate-release solid oral dosage form. After a single dose of 5 mg/kg in adults, a mean peak serum concentration of about 10 mcg/mL (range 5–15 mcg/mL) can be expected 1–2 hours after the dose. Co-administration of theophylline with food or antacids does not cause clinically significant changes in the absorption of theophylline from immediate-release dosage forms.

Continued on next page

100 mcg, yellow
Bottles of 100, Code 3P1073 NDC 0048-1070-03
Bottles of 1000, Code 3P1075 NDC 0048-1070-05
Unit Dose Cartons of 100, Code 3P1063 NDC 0048-1070-13
112 mcg, rose
Bottles of 100, Code 3P1183 NDC 0048-1080-03
Bottles of 1000, Code 3P1185 NDC 0048-1080-05
125 mcg, brown
Bottles of 100, Code 3P1103 NDC 0048-1130-03
Bottles of 1000, Code 3P1105 NDC 0048-1130-05
Unit Dose Cartons of 100, Code 3P1113 NDC 0048-1130-13
150 mcg, blue
Bottles of 100, Code 3P1093 NDC 0048-1090-03
Bottles of 1000, Code 3P1095 NDC 0048-1090-05
Unit Dose Cartons of 100, Code 3P1083 NDC 0048-1090-13
175 mcg, lilac
Bottles of 100, Code 3P1153 NDC 0048-1100-03
200 mcg, pink
Bottles of 100, Code 3P1143 NDC 0048-1140-03
Bottles of 1000, Code 3P1145 NDC 0048-1140-05
Unit Dose Cartons of 100, Code 3P1133 NDC 0048-1140-13
300 mcg, green
Bottles of 100, Code 3P1173 NDC 0048-1170-03
Bottles of 1000, Code 3P1175 NDC 0048-1170-05

Store at controlled room temperature 15°–30°C (59°–86°F). SYNTHROID Tablets should be protected from light and moisture.

SYNTHROID* (Levothyroxine Sodium, USP) Injection is a lyophilized powder. It is supplied in color coded vials as follows:

200 mcg, gray
10 mL Single Dose Vial, Code 3P1312 NDC 0048-1014-99
500 mcg, yellow
10 mL Single Dose Vial, Code 3P1302 NDC 0048-1012-99

Store at controlled room temperature 15°–30°C (59°–86°F).

DIRECTIONS FOR RECONSTITUTION

Reconstitute the lyophilized levothyroxine sodium by aseptically adding 5 mL of 0.9% Sodium Choride Injection, USP or Bacteriostatic Sodium Chloride Injection, USP with Benzyl Alcohol (final volume approximately 5 mL). Shake vial to ensure complete mixing. Do not add to other intravenous fluids. Discard any unused portion.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

*Tablets Manufactured by
BASF Pharmaceuticals
A Unit of BASF
Humacao, Puerto Rico 00664
Injection Manufactured by
Ben Venue Laboratories, Inc.
Bedford, Ohio 44146 USA

3520-07 Rev. 05/24/95

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EDUCATIONAL MATERIAL

"Treatment of Hypothyroid Disease in the Elderly" (2 credits) Home Study Module-Pharmacists

Kramer Laboratories, Inc.
8778 S.W. 8TH STREET
MIAMI, FL 33174

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[redacted]824-4894
Medical Information Contact:
Emergencies:
Professional Director
[redacted]824-4894

CHARCOAL PLUS DS® ENTERIC COATED OTC

250 mg Activated Charcoal Tablets

After every meal

RECOMMENDED CONSUMPTION

Two enteric coated tablets after eating as needed but do not exceed 20 tablets per day. Swallow the tablets whole. Do not chew.

CAUTION

If taking medication allow an interval of 1 hour between ingestion of this product and ingestion of any medication.

HOW SUPPLIED

Bottles of 120 tablets and 36 tablets.

WARNING

Activated Charcoal may cause darkening of the stool.

HALFPRIN® OTC

162 mg. Enteric Coated Aspirin
Aspirin For Suspected Acute MI

DESCRIPTION

Halfprin® is the only 162 mg. enteric coated aspirin available for the indicated use to reduce the risk of vascular mortality in people with a suspected acute myocardial infarction (MI). The Halfprin® 162 mg. aspirin has been determined to be the indicated dose to reduce the risk of fatal and nonfatal cardiovascular and cerebrovascular events in subjects with a suspected acute MI.

INDICATIONS

Suspected Acute MI

The use of aspirin in patients with a suspected acute MI is supported by the results of a large, multicenter 2×2 factorial study of 17,187 subjects with suspected acute MI.(1). Subjects were randomized within 24 hours of the onset of symptoms so that 8,57 subjects received oral aspirin (162.5 milligrams, enteric-coated) daily for 1 month (the first dose crushed, sucked, or chewed) and 8,600 received oral placebo. Of the subjects 8,592 were also randomized to receive a single dose of streptokinase (1.5 million units) infused intravenously for about 1 hour, and 8,595 received a placebo infusion. Thus, 4,295 subject received aspirin plus placebo, 4,300 received streptokinase plus placebo, 4,292 received aspirin plus streptokinase, and 4,300 received double placebo.

Vascular mortality (attributed to cardiac, cerebral, hemorrhagic, other vascular, or unknown causes) occurred in 9.4 percent of subjects in the aspirin group and in 11.8 percent of subjects in the oral placebo group in the 35-day follow up. This represents an absolute reduction of 2.4 percent in the mean 35-day vascular mortality attributable to aspirin and a 23 percent reduction in odds of vascular death.

Significant absolute reductions in mortality and corresponding reductions in specific clinical events favoring aspirin were found for reinfarction (1.5 percent absolute reduction, 45 percent odds reduction, $2p < 0.00001$), cardiac arrest (1.2 percent absolute reduction, 14.2 percent odds reduction, $2p < 0.01$), and total stroke (0.4 percent absolute reduction, 41.5 percent odds reduction, $2p < 0.01$). The effect of aspirin over and above its effect on mortality was evidenced by small, but significant, reductions in vascular morbidity in those subjects who were discharged.

The beneficial effects of aspirin on mortality were present with or without streptokinase infusion. Aspirin reduced vascular mortality from 10.4 to 8.0 percent for days 0 to 35 in subjects given streptokinase and reduced vascular mortality from 13.2 to 10.7 percent in the effects of aspirin and thrombolytic therapy with streptokinase in this study were approximately additive. Subjects who received the combination of streptokinase infusion and daily aspirin had significantly lower vascular mortality at 35 days than those who received either active treatment alone (combination 8.0 percent, aspirin 10.7 percent, streptokinase 10.4 percent, and no treatment 13.2 percent. While this study demonstrated that aspirin has an additive benefit in patients given streptokinase, there is no reason to restrict its use to that specific thrombolytic.

ADVERSE REACTIONS

Gastrointestinal Reactions

Doses of 1,000 milligrams per day of aspirin caused gastrointestinal symptoms and bleeding that in some cases were clinically significant. In the Aspirin Myocardial Infarction Study (AMIS) (4) with 4,500 post infarction subjects, the percentage incidences of gastrointestinal symptoms for the aspirin (1,000 milligrams of a standard, solid—tablet formulation) and placebo-treated subjects, respectively, were: Stomach pain (14.5 percent, 4.4 percent); heartburn (11.9 percent, 4.8 percent); nausea and/or vomiting (7.6 percent; 2.1 percent); hospitalization for gastrointestinal disorder (4.8 percent, 3.5 percent). Symptoms and signs of gastrointestinal irritation were not significantly increased in subjects treated for instable angina with 325 milligrams buffered aspirin in solution.

Bleeding

In the AMIS and other trails, aspirin treated subjects had increased rates of gross gastrointestinal bleeding. In the ISIS—2 study (1), there was no significant difference in the incidence of major bleeding (bleeds requiring transfusion) between 8,587 subjects taking 162.5 milligrams aspirin daily and 8,600 subjects taking placebo (31 versus 33 subjects). There were five confirmed cerebral hemorrhage in the aspirin group compared with two in the placebo group, but the incidence of stroke of all causes was significantly reduced from 81 to 47 for the placebo versus aspirin group (0.4 percent absolute change). There was a small and statistically significant excess (0.6 percent) of minor bleeding in people taking aspirin (2.5 percent for aspirin, 1.9 percent for placebo). No other significant adverse effects were reported.

Cardiovascular and Biochemical

In the AMIS trail(4), the dosage of 1,000 milligrams per day of aspirin was associated with small increases in systolic blood pressure (BP) (average 1.5 to 2.1 millimeters Hg) and diastolic BP (0.5 to 0.6 millimeters Hg), depending upon whether maximal or last available readings were used. Blood urea nitrogen and uric acid levels were also increased, but by less than 1.0 milligram percent.

Subjects with marked hypertension or renal insufficiency had been excluded from the trail so that clinical importance of these observations for such subjects or for any subjects treated over more prolonged periods is not known. It is recommended that patients placed on long-term aspirin treatment, even at doses of 160 milligrams per day, be seen at regular intervals to assess changes in these measurements.

DOSAGE AND ADMINISTRATION

The recommended dose of aspirin to treat suspected acute MI is 160 to 162.5 milligrams taken as soon as the first infarct is suspected and then daily for at least 30 days. (One-half of a conventional 325-milligram aspirin tablet or two 80–81 milligram aspirin tablets may be taken.) This use of aspirin applies to both solid, oral dosage forms (buffered, plain, and enteric-coated aspirin) and buffered aspirin in solution. If using a solid dosage form, the first dose should be crushed, sucked, or chewed. After the 30-day treatment, physicians should consider further therapy based on the labeling for dosage and administration of aspirin for prevention of recurrent MI (reinfarction).

REFERENCES

(1) ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. "Randomized Trail of Intravenous Streptokinase, Oral Aspirin, Both, or Neither Among 17,187 Cases of Suspected Acute Myocardial Infarction: ISIS-2," lancet, 2:349–360, August 13, 1988.

HOW SUPPLIED

Halfprin Tablets
162 mg. in bottle of 60* and 200
81 mg. in bottle of 90
*Easy to open bottle/ Not child-resistant caps.

Comments questions or sample request call toll free 1-800-824-4894

SAFE TUSSIN 30 OTC

EXPECTORANT/COUGH SUPPRESSANT

DESCRIPTION

Each 10 cc contains 200 mg Guaifenesin, U.S.P. and 30 mg Dextromethorphan Hydrobromide U.S.P.

INDICATIONS

For temporary relief of cough due to minor throat and bronchial irritation associated with the common cold or inhaled irritants. Helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus.

DIRECTIONS

Adults and children 12 years of age and over: 2 teaspoonfuls every 6 hours, not to exceed 8 teaspoonfuls in 24 hours. Children 6 to under 12 years of age: 1 teaspoonful every 6 hours not to exceed 4 teaspoonfuls in 24 hours. Children 2 to under 6 years of age: ½ teaspoonful every 6 hours not to exceed 2 teaspoonfuls in 24 hours. Children under 2 years of age consult a physician.

INACTIVE INGREDIENTS

Citric Acid, Benzoic Acid U.S.P., Glycerin U.S.P., Sorbitol, Flavor (Peppermint, Menthol), Water.

Safe Tussin 30 does not contain antihistamines, sugar, alcohol, sodium, dyes, codeine; all of which may pose risks for certain patients. Each dose of Safe Tussin 30 contains .066g sorbitol, a non-nutritive caloric sweetener.

Continued on next page

Kramer Laboratories—Cont.

CONTRAINDICATIONS
Do not take if hypersensitive to Guaifenesin, Dextromethorphan or any of the ingredients listed above.

HOW SUPPLIED
Clear liquid in 4 oz bottles.

YOHIMEX™ Tablets ℞
[*yō-him 'eks*]

DESCRIPTION
Each tablet for oral administration contains yohimbine hydrochloride, 5.4 mg. ($^1/_{12}$ grain). Yohimbine is an indoalkylamine alkaloid with chemical similarity to reserpine. It is the principal alkaloid of the bark of the West African Corynanthe yohimbe tree and is also found in Rauwolfia Serpentina (L) Benth.

ACTIONS
Yohimbine is primarily an alpha-2 adrenergic blocker, which blocks presynaptic alpha-2-adrenoreceptors.
PHARMACOLOGY: Its peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. In male sexual performance, erection is linked to cholinergic activity which theoretically results in increased penile blood inflow, decreased penile blood outflow or both, causing erectile stimulation without increasing sexual desire. Yohimbine exerts a stimulating action on mood and may increase anxiety. Such actions are not adequately studied, although they appear to require high doses. Yohimbine has a mild antidiuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. The drug reportedly exerts no significant influence on cardiac stimulation and other effects mediated by beta-adrenergic receptors.

INDICATIONS
Sympathicolytic and mydriatic agent. Impotence has been successfully treated with yohimbine in male patients with vascular or diabetic origins and psychogenic origins (18 mg./day). Urologists have used yohimbine experimentally for the treatment and the diagnostic classification of certain types of male erectile impotence.

CONTRAINDICATIONS
In patients with renal disease; hypersensitivity to any component.

WARNINGS
Not for use in geriatric patients, psychiatric patients or cardio-renal patients with a history of gastric or duodenal ulcer. Generally not for use in females.
USAGE IN PREGNANCY: Do not use during pregnancy.
USAGE IN CHILDREN: Do not use in children.

DRUG INTERACTIONS
Do not use yohimbine with antidepressants and other mood-modifying drugs.

ADVERSE REACTIONS
CNS: Yohimbine readily penetrates the CNS and produces a complex pattern of responses in doses lower than those required to produce peripheral alpha-adrenergic blockade. These include: antidiuresis and central excitation including elevated blood pressure and heart rate, increased motor activity, nervousness, irritability and tremor. Dizziness, headache and skin flushing have been reported.

OVERDOSAGE
Daily doses of 20–30 mg. may produce increases in heart rate and blood pressure, piloerection and rhinorrhea. More severe symptoms may include paresthesias, incoordination, tremulousness and a dissociative state with higher doses.

DOSAGE AND ADMINISTRATION
USUAL ADULT DOSE: One tablet taken 3 times daily. If side effects occur, the dosage is to be reduced to ½ tablet 3 times a day followed by gradual increase to 1 tablet 3 times a day. The therapy reported is not more than 10 weeks.

HOW SUPPLIED
Pink, round tablets in bottles of 100 tablets (NDC 55505-100-15)

Laser, Inc.
2200 W. 97TH PLACE, P.O. BOX 905
CROWN POINT, IN 46307

Direct Inquiries to:
Joseph N. Allegretti, R.Ph.
(219) 663-1165

DALLERGY® CAPLETS, SYRUP, TABLETS ℞

Each Extended-Release Caplet* (Capsule-shaped tablet) contains: Chlorpheniramine Maleate 8 mg, Phenylephrine Hydrochloride 20 mg, Methscopolamine Nitrate 2.5 mg. Each 5 mL of grape-flavored Syrup contains: Chlorpheniramine Maleate 2 mg, Phenylephrine Hydrochloride 10 mg, Methscopolamine Nitrate 0.625 mg. Each Tablet contains: Chlorpheniramine Maleate 4 mg, Phenylephrine Hydrochloride 10 mg, Methscopolamine Nitrate 1.25 mg.
*In a specially prepared base to provide a prolonged therapeutic effect.

DALLERGY® –JR. CAPSULES ℞

Each Extended-Release Capsule* contains: Brompheniramine Maleate 6 mg, Pseudoephedrine Hydrochloride 60 mg.
*In a specially prepared base to provide prolonged action.

DONATUSSIN DC SYRUP Ⓒ ℞

Each 5 mL contains: Hydrocodone* Bitartrate 2.5 mg *(WARNING: May be habit forming), Phenylephrine Hydrochloride 7.5 mg, Guaifenesin 50 mg. Red Syrup.

DONATUSSIN DROPS ℞

Each mL contains: Chlorpheniramine Maleate 1 mg, Phenylephrine Hydrochloride 2 mg, Guaifenesin 20 mg.
Peach-flavored, orange color.

DONATUSSIN SYRUP ℞

Each 5 mL contains: Dextromethorphan HBr 7.5 mg, Chlorpheniramine Maleate 2 mg, Phenylephrine HCl 10 mg, Guaifenesin 100 mg. Red Syrup.

FUMATINIC® CAPSULES ℞

Each Extended-Release FUMATINIC Capsule contains: Ferrous Fumarate* 275 mg (equivalent to 90 mg of elemental iron), Vitamin C* (Ascorbic Acid) 100 mg, Vitamin B-12 (Cyanocobalamin) 15 mcg, Folic Acid 1 mg.
*In a specially prepared base to provide prolonged action.

KIE® SYRUP ℞

Each 5 mL contains: Potassium Iodide 150 mg, Ephedrine Hydrochloride 8 mg. Green Syrup.

LACTOCAL-F TABLETS ℞

Multivitamin, Multimineral supplement for pregnant or lactating women. White coated dye free tablet.

RESPAIRE®-SR CAPSULES 60 & 120 ℞

Each Extended-Release RESPAIRE-60 SR Capsule contains: Pseudoephedrine Hydrochloride* 60 mg and Guaifenesin† 200 mg. Each Extended-Release RESPAIRE-120 SR Capsule contains: Pseudoephedrine Hydrochloride* 120 mg and Guaifenesin† 250 mg.
*In a specially prepared base to provide prolonged action.
†Designed for immediate release to provide rapid action.

Lederle Piperacillin, Inc.
CAROLINA, PUERTO RICO 00630

Lederle Oncology
A Division of American Cyanamid Co.
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WAYNE, NJ 07470

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METHOTREXATE Sodium for Injection
METHOTREXATE LPF® Sodium (METHOTR... Sodium Injection)
METHOTREXATE Sodium Injection
NOVANTRONE® Mitoxantrone for Injection Concentrate
THIOTEPA For Injection Sterile 15 mg/Vial

For more information on these products, please see under Immunex on p.1312 of this 1997 edition of th...

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Night: (610) 688-4400 (Emergencies only; non-emer... should wait until the next day)

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LEDERLE PRODUCTS

The following list of Lederle products includes the al... meric LEDERMARK® codes which provide quick a... tive identification of Lederle capsules and tablets:

Product Identity Code No.	Product
	ACEL-IMUNE® Diphtheria and Tetan... oids and Acellular Pertussis Vaccine Ad...
A11	ARTANE® Tabs., 2mg
A12	ARTANE® Tabs., 5mg
—	ARTANE® Elixir, 2mg/5mL
A13	ASENDIN® Tabs., 25mg
A15	ASENDIN® Tabs., 50mg
A17	ASENDIN® Tabs., 100mg
A18	ASENDIN® Tabs., 150mg
B1	ZEBETA® Tablets, 5mg
B3	ZEBETA® Tablets, 10mg
B12	ZIAC® Tablets, 2.5/6.25mg

Directions for Use of the LEDERJECT Disposable Syringe:

1. Twist the plunger rod clockwise to be sure the rod is secure to rubber plunger base.
2. Hold needle shield in place with index finger and thumb of one hand while, with the other thumb, exert light pressure on plunger rod until the plunger base has been freed and demonstrates slight movement when pressure is applied.
3. Grasp the rubber needle shield at its base; twist and pull to remove.
4. To prevent needle-stick injuries, needles should not be recapped, purposely bent, or broken by hand.

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LEDERLE LABORATORIES DIVISION
American Cyanamid Company
Pearl River, NY 10965

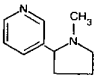
Shown in Product Identification Guide, page 321

PROSTEP®

(nicotine transdermal system)
Systemic delivery of 22 or 11 mg/day over 24 hours

DESCRIPTION

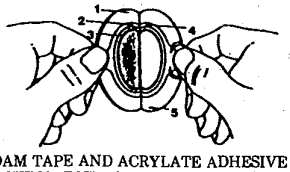
PROSTEP is a transdermal system that provides systemic delivery of nicotine following its application to intact skin. Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a colorless to pale yellow, freely water-soluble, strongly alkaline, oily, volatile, hygroscopic liquid obtained from the tobacco plant. Nicotine has a characteristic pungent odor and turns brown on exposure to air or light. Of its two stereoisomers, *S* (-)-nicotine is the more active. It is the prevalent form in tobacco, and is the form in the PROSTEP system. The free alkaloid is absorbed rapidly through the skin and respiratory tract.



Chemical Name:
S-3-(1-methyl-2-pyrrolidinyl) pyridine
Molecular Formula: $C_{10}H_{14}N_2$
Molecular Weight: 162.23
Ionization Constants: $pK_{a1}=7.84$, $pK_{a2}=3.04$
Octanol-Water Partition Coefficient: 15.1 at pH 7

The PROSTEP system is a round, flat, adhesive pad with a round well in the center containing nicotine (the active agent) in a hydrogel matrix. Proceeding from the visible outer surface toward the inner surface attached to the skin are: (1) a beige-colored foam tape and pressure-sensitive acrylate adhesive; (2) backing foil, gelatin and low-density polyethylene; (3) nicotine-gel matrix; (4) protective foil with well and (5) release liner which overlies the adhesive layer and must be removed prior to use. PROSTEP systems are packaged in child-resistant pouches.

STICKY SIDE: APPLY TO SKIN — NONSTICKY SIDE: DISCARD



1— FOAM TAPE AND ACRYLATE ADHESIVE
2— BACKING FOIL, GELATIN AND LOW DENSITY POLYETHYLENE COATING
3— NICOTINE-GEL MATRIX
4— PROTECTIVE FOIL WITH WELL
5— RELEASE LINER

Nicotine is the active ingredient; other components of the system are pharmacologically inactive.

The amount of nicotine delivered to the patient from each system (130 mcg/cm^2-h) is proportional to the surface area of the nicotine-gel matrix. About 27% of the total amount of nicotine remains in the system 24 hours after application. PROSTEP systems are labelled with the average dose absorbed by the patient. The dose of nicotine absorbed from a PROSTEP system represents 98% of the amount released from the system in 24 hours.

Dose Absorbed in 24 hrs (mg/day)	System Surface Area (cm^2)	Total Nicotine Content (mg)	Residual Nicotine after 24 hrs (mg)
22	7	30	8
11	3.5	15	4

CLINICAL PHARMACOLOGY

Pharmacologic Action

Nicotine, the chief alkaloid in tobacco products, binds stereoselectively to acetylcholine receptors at the autonomic ganglia, in the adrenal medulla, at neuromuscular junctions, and in the brain. Two types of central nervous system effects are believed to be the basis of nicotine's positively reinforcing properties. A stimulating effect, exerted mainly in the cortex via the locus ceruleus, produces increased alertness and cognitive performance. A "reward" effect via the "pleasure system" in the brain is exerted in the limbic system. At low doses the stimulant effects predominate while at high doses the reward effects predominate. Intermittent intravenous administration of nicotine activates neurohormonal pathways, releasing acetylcholine, norepinephrine, dopamine, serotonin, vasopressin, beta-endorphin, growth hormone, and ACTH.

Pharmacodynamics

The cardiovascular effects of nicotine include peripheral vasoconstriction, tachycardia, and elevated blood pressure. Acute and chronic tolerance to nicotine develops from smoking tobacco or ingesting nicotine preparations. Acute tolerance (a reduction in response for a given dose) develops rapidly (less than 1 hour) but not at the same rate for different physiologic effects (skin temperature, heart rate, subjective effects). Withdrawal symptoms, such as cigarette craving, can be reduced in some individuals by plasma nicotine levels lower than those from smoking.

Withdrawal from nicotine in addicted individuals is characterized by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbances, impaired concentration, increased appetite, minor somatic complaints (headache, myalgia, constipation, fatigue), and weight gain. Nicotine toxicity is characterized by nausea, abdominal pain, vomiting, diarrhea, diaphoresis, flushing, dizziness, disturbed hearing and vision, confusion, weakness, palpitations, altered respirations and hypotension.

The cardiovascular effects of PROSTEP 22 mg/day systems include slight increase in heart rate and blood pressure. The cardiovascular effects of applying one or two PROSTEP 22 mg/day systems used continuously for 24 hours were compared to placebo for 7 days. Changes in heart rate (increased 4 beats/min), systolic blood pressure (increased 4 mmHg) and diastolic blood pressure (increased 3 mmHg) were observed.

Both smoking and nicotine can increase circulating cortisol and catecholamines, and tolerance does not develop to the catecholamine-releasing effects of nicotine. Changes in the response to a concomitantly administered adrenergic agonist or antagonist should be watched for when nicotine intake is altered during nicotine replacement therapy with PROSTEP systems (see **Drug Interactions**).

Pharmacokinetics

Following application of the PROSTEP system to the upper body or upper outer arm, virtually all of the nicotine released from the system enters the systemic circulation. All PROSTEP systems are labelled as to the average amount of nicotine absorbed by patients.

The volume of distribution following IV administration of nicotine is approximately 2 to 3 L/kg and the half-life ranges from 1 to 2 hours. The major eliminating organ is the liver, and average plasma clearance is about 1.2 L/min; the kidney and lung also metabolize nicotine. There is no significant skin metabolism of nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound. The primary metabolite of nicotine in plasma, cotinine, has a half-life of 15 to 20 hours and concentrations that exceed nicotine by 10-fold.

Plasma protein binding of nicotine is <5%. Therefore changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have significant effects on nicotine kinetics.

The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxycotinine (45% of the dose). Usually about 10% of nicotine is excreted unchanged in the urine. As

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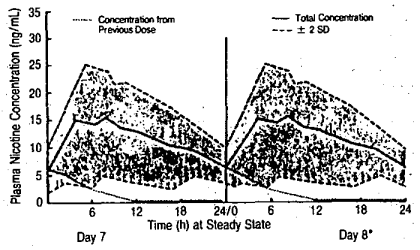
much as 30% may be excreted unchanged in the urine with high urine flow rates and acidification below pH 5.

The pharmacokinetic model which best fits the plasma nicotine concentrations from PROSTEP systems is an open, two compartment model with a skin depot through which nicotine enters the central disposition compartment.

The PROSTEP system gel matrix contacts the skin directly and acts as a reservoir from which nicotine is absorbed slowly over the 24 hours.

Steady-State Plasma Nicotine Concentrations for Two Consecutive Applications of PROSTEP 22 mg/day (Mean ± 2 SD, N=22)



*Day 8 is a reproduction of Day 7 data to represent steady-state dosing.

Following application of a system, nicotine concentrations increase to a peak between 4 and 12 hours and then decrease gradually (see graph). Steady state for nicotine is attained within 2 days of initiating PROSTEP treatment and plasma nicotine concentrations average 23% higher compared to single-dose application. Plasma nicotine concentrations are proportional to dose (i.e., linear kinetics are observed) for the two dosages of PROSTEP systems. Nicotine kinetics are similar for all sites of application on the upper torso and upper outer arm.

Following removal of PROSTEP systems, plasma nicotine concentrations decline in an exponential fashion with an apparent mean half-life of 3 to 4 hours due to continued absorption from the skin depot (see dotted line in figure) in contrast to a half-life of 1–2 hours following IV administration. Most nonsmoking patients will have nondetectable nicotine concentrations in 10 to 12 hours after patch removal.

Steady State Nicotine Pharmacokinetic Parameters for 22 mg/day PROSTEP Systems (mean, std dev, range)

Parameter (units)	22 mg/day (N=22) Mean	SD	Range
C_{max} (ng/mL)	16	6	7–31
C_{avg} (ng/mL)	11	3	6–17
C_{min} (ng/mL)	5	1	3–9
T_{max} (hrs)	9	5	4–24

C_{max}: maximum observed plasma concentration
C_{avg}: average plasma concentration
C_{min}: minimum observed plasma concentration
T_{max}: time of maximum plasma concentration

CLINICAL TRIALS

The efficacy of PROSTEP treatment as an aid to smoking cessation was demonstrated in two placebo-controlled, double-blind trials in otherwise healthy patients smoking at least one pack per day (N=516). In one of these trials, PROSTEP therapy was combined with concomitant individual patient counseling (10 minutes each visit) and in the other trial PROSTEP therapy was used with group counseling (1 hour each visit). In both trials, patients were treated for 8 weeks with a fixed dosage of 22 mg/day or placebo followed by abrupt cessation of PROSTEP treatment and decrease in support therapy. Patients in these two trials received prestudy counseling at two visits before beginning treatment. Two earlier trials (N=409) were carried out without prestudy counseling with treatment for 6 weeks and weaning to the 11 mg/day patch in one of them (N=329). In all four trials quitting was defined as total abstinence from smoking as measured by patient diary and verified by expired carbon monoxide. The "quit rates" are the proportions of all persons initially enrolled who abstained after week 2.

Quit Rates by Treatment After Week 2 (range by clinics)*

Nicotine Treatment	Number of Patients	After 6 Weeks	After 6 Months
PROSTEP (22 mg/day)	259	10%–57%	0%–37%
Placebo	257	3%–30%	0%–20%

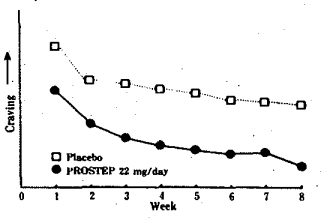
*Trial involved 7 clinics, number of patients per treatment ranged from 29 to 60.

The two trials with prestudy counseling demonstrated that with concomitant support, fixed dosage therapy with PROSTEP therapy was more effective than placebo after 6 weeks and data from these 2 studies are combined in the quit rate table. At 8 weeks, just prior to abrupt termination of PROSTEP treatment (no weaning), quit rates were 6%–50%. At follow-up, three to five days later, quit rates were 3%–50%. In the two other studies without prestudy counseling, quit rates of 0%–46% with PROSTEP 22 mg/day and 3%–31% with placebo were observed at 6 weeks. In each of the four studies, there was a large variation in quit rates among clinics for each treatment.

Patients using PROSTEP systems dropped out of the trials significantly less frequently than did patients receiving placebo (26% vs 34%). The quit rate for 30 patients over age 60 was comparable to the quit rate for 486 patients aged 60 and under.

Patients who used the 22 mg/day PROSTEP treatment in clinical trials had a significant reduction in craving for cigarettes (desire to smoke), a major nicotine withdrawal symptom, as compared to placebo-treated patients (see figure). Reduction in craving, as with quit rate, is quite variable. This variability from clinic to clinic is presumed to be due to inherent differences in patient populations, e.g., patient motivation, concomitant illnesses, number of cigarettes smoked per day, number of years smoking, exposure to other smokers, socioeconomic status, etc., as well as differences among the clinics.

Severity of Craving by Treatment from Clinical Trials (N=516)



Individualization of Dosage

It is important to make sure that patients read the instructions made available to them and have their questions answered. They should clearly understand the directions for applying and disposing of PROSTEP systems. They should be instructed to stop smoking completely when the first PROSTEP system is applied.

The success or failure of smoking cessation depends heavily on the quality, intensity, and frequency of supportive care. Patients are more likely to quit smoking if they are seen frequently and participate in formal smoking cessation programs.

The goal of PROSTEP therapy is complete abstinence. Significant health benefits have not been demonstrated for reduction of smoking. If a patient is unable to stop smoking by the fourth week of therapy, treatment should probably be discontinued. Patients who have not stopped smoking after four weeks of PROSTEP therapy are unlikely to quit on that attempt.

Patients who fail to quit on any attempt may benefit from interventions to improve their chances for success on subsequent attempts. Patients who were unsuccessful should be counseled to determine why they failed. Patients should then probably be given a "therapy holiday" before the next attempt. A new quit attempt should be encouraged when the factors that contributed to failure can be eliminated or reduced, and conditions are more favorable.

Based on the clinical trials, a reasonable approach to assisting patients in their attempt to quit smoking is to initiate therapy with PROSTEP 22 mg/day except for small patients less than 100 pounds (see **DOSING SCHEDULE** below). The need for dose adjustment should be assessed during the first 2 weeks. The symptoms of nicotine withdrawal and toxicity overlap (see **Pharmacodynamics** and **ADVERSE REACTIONS** sections). Since patients using PROSTEP treatment may also smoke intermittently, it may be difficult to determine if patients are experiencing nicotine withdrawal or nicotine excess.

The controlled clinical trials using PROSTEP therapy suggest that sweating, abdominal pain, and somnolence are more often symptoms of nicotine excess while irritability is more often a symptom of nicotine withdrawal.

Patients should continue the dose selected with counseling and support over the following month. Those who have successfully stopped smoking during that time can stop PROSTEP treatment or may be weaned (reduction to 11 mg/day) over 4 weeks, after which treatment should be terminated.

DOSING SCHEDULE

	Patients ≥ 100 lbs.	Patients < 100 lbs.
Initial/Starting Dose	22 mg/day	11 mg/day
Duration of Treatment	4–8 weeks	4–8 weeks
Optional Weaning Dose	11 mg/day	off
Duration of Treatment	2–4 weeks	

INDICATIONS AND USAGE

PROSTEP treatment is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. PROSTEP treatment should be used as a part of a comprehensive behavioral smoking cessation program.

The use of PROSTEP systems for longer than 3 months has not been studied.

CONTRAINDICATIONS

Use of PROSTEP systems is contraindicated in patients with hypersensitivity or allergy to nicotine or to any of the components of the therapeutic system.

WARNINGS

Nicotine from any source can be toxic and addictive. Smoking causes lung cancer, heart disease, emphysema, and may adversely affect the fetus and the pregnant woman. For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking-cessation program should be weighed against the hazard of continued smoking while using PROSTEP systems, and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy Warning

Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. Nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that PROSTEP treatment can cause fetal harm when administered to a pregnant woman. The effect of nicotine delivery by PROSTEP systems has not been examined in pregnancy (see **PRECAUTIONS**). Therefore pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches. If PROSTEP therapy is used during pregnancy, or if the patient becomes pregnant while using PROSTEP treatment, the patient should be apprised of the potential hazard to the fetus.

Safety Note Concerning Children

The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if PROSTEP systems are applied or ingested by children or pets. Used 22 mg/day systems contain about 27% (8 mg) of their initial drug content. Therefore, patients should be cautioned to keep both used and unused PROSTEP systems out of the reach of children and pets.

PRECAUTIONS

The patient should be urged to stop smoking completely when initiating PROSTEP therapy (see **DOSAGE AND ADMINISTRATION**). Patients should be informed that if they continue to smoke while using PROSTEP systems, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the PROSTEP dose should be reduced or PROSTEP treatment discontinued (see **WARNINGS**). Physicians should anticipate that concomitant medications may need dosage adjustment (see **Drug Interactions**). The use of PROSTEP systems beyond 3 months by patients who stop smoking should be discouraged because the chronic consumption of nicotine by any route can be harmful and addicting.

Allergic Reactions

In a 3-week open-label dermal irritation and sensitization study of PROSTEP systems, 16 of 205 patients (8%) exhibited definite erythema at 24 hours after system removal. None of those patients exhibited contact allergy. In the first 4 weeks of the efficacy trials, moderate erythema following system removal was seen in 22% of patients, some edema in 8%, and dropouts due to skin reactions occurred in 7% of 459 patients using the 22 mg/day system. Patients who develop contact sensitization should be cautioned that a serious reaction

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could occur from exposure to other nicotine-containing products or smoking.

Patients should be instructed to promptly discontinue the PROSTEP treatment and contact their physician if they experience severe or persistent local skin reactions at the site of application (e.g., severe erythema, pruritus or edema) or a generalized skin reaction (e.g., urticaria, hives, or generalized rash).

Skin Disease

PROSTEP systems are usually well tolerated by patients with normal skin, but may be irritating for patients with some skin disorders (atopic or eczematous dermatitis).

Cardiovascular or Peripheral Vascular Diseases

The risks of nicotine replacement in patients with certain cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina) should be carefully screened and evaluated before nicotine replacement is prescribed.

Tachycardia occurring in association with the use of PROSTEP treatment was reported occasionally. If serious cardiovascular symptoms occur with PROSTEP treatment, it should be discontinued.

PROSTEP treatment should generally not be used in patients during the immediate post-myocardial infarction period, patients with serious arrhythmias, and patients with severe or worsening angina pectoris.

Renal or Hepatic Insufficiency

The pharmacokinetics of nicotine have not been studied in the elderly or patients with renal or hepatic impairment. However, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation (see **Pharmacokinetics**).

Endocrine Diseases

PROSTEP treatment should be used with caution in patients with hyperthyroidism, pheochromocytoma, or insulin-dependent diabetes since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease

Nicotine delays healing in peptic ulcer disease; therefore, PROSTEP treatment should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Accelerated Hypertension

Nicotine constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, PROSTEP treatment should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Information for Patient

A patient instruction sheet is included in the package of PROSTEP systems dispensed to the patient. It contains important information and instructions on how to use and dispose of PROSTEP systems properly. Patients should be encouraged to ask questions of the physician and pharmacist. Patients must be advised to keep both used and unused systems out of the reach of children and pets.

Drug Interactions

Smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications.

[See table above.]

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidences of tumors in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumor-initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

Neither nicotine nor cotinine were mutagenic in the Ames *Salmonella* test. Nicotine induced repairable DNA damage in an *E. coli* test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

PREGNANCY

Pregnancy Category D (see WARNINGS section)

The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, an increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of PROSTEP treatment on fetal development are unknown. Therefore pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

PROSTEP treatment should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of use of nicotine replacement by the patient, who may continue to smoke.

Teratogenicity

Animal Studies: Nicotine was shown to produce skeletal abnormalities in the offspring of mice when given doses toxic to the dams (25 mg/kg IP or SC).

Human Studies: Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

Other Effects

Animal Studies: A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension (fetal and maternal concentrations were about 20 times those achieved after smoking one cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking one cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 mg/kg/min nicotine for 20 minutes to pregnant rhesus monkeys (equivalent to smoking about six cigarettes every minute for 20 minutes).

Human Experience: Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low birth weight infants and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effects of cigarette smoking on fetal cardiovascular parameters have been studied near term. Cigarettes increased fetal aortic blood flow and heart rate and decreased uterine blood flow and fetal breathing movements. PROSTEP treatment has not been studied in pregnant humans.

Labor and Delivery

PROSTEP systems are not recommended to be left on during labor and delivery. The effects of nicotine on the mother or the fetus during labor are unknown.

Use in Nursing Mothers

Caution should be exercised when PROSTEP therapy is administered to nursing women. The safety of PROSTEP treatment in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk to plasma ratio averages 2.9. Nicotine is absorbed orally. An infant has the ability to clear nicotine by hepatic first pass clearance; however the efficiency of removal is probably lowest at birth. The nicotine concentrations in milk can be expected to be lower with PROSTEP treatment when used as directed than with cigarette smoking, as maternal plasma nicotine concentrations are generally reduced with nicotine replacement. The risk of exposure of the infant to nicotine from PROSTEP systems should be weighed against the risks associated with the infant's exposure to nicotine from continued smoking by the mother (passive smoke exposure and contamination of breast milk with other components of tobacco smoke) and from PROSTEP systems alone or in combination with continued smoking.

Pediatric Use

PROSTEP systems are not recommended for use in children because the safety and effectiveness of PROSTEP treatment in children and adolescents who smoke have not been evaluated.

May Require a Decrease in Dose at Cessation of Smoking	Possible Mechanism
acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, theophylline	Deinduction of hepatic enzymes on smoking cessation
insulin	Increase of subcutaneous insulin absorption with smoking cessation
adrenergic antagonists (e.g., prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation

May Require an Increase in Dose at Cessation of Smoking	Possible Mechanism
adrenergic agonists (e.g., isoproterenol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation

Geriatric Use

Thirty patients over the age of 60 participated in clinical trials of PROSTEP therapy. PROSTEP therapy appeared to be as effective in this age group as in younger smokers.

ADVERSE REACTIONS

Assessment of adverse events in the 903 patients who participated in controlled clinical trials is complicated by the occurrence of GI and CNS effects of nicotine withdrawal as well as nicotine excess. The actual incidences of both are confounded by concurrent smoking by many of the patients. In the trials, when reporting adverse events, the investigators did not attempt to identify the cause of the symptom.

Topical Adverse Events

The most common adverse event associated with topical nicotine is a mild short-lived erythema, pruritus, or burning at the application site, which was seen at least once in 54% of patients (N=459) on PROSTEP treatment in the 6–8 week clinical trials. Local erythema after system removal was noted at least once in 22% of patients and local edema in 8%. Erythema generally resolved within 24 hours. Cutaneous hypersensitivity (contact sensitization) occurred in 3% of patients on PROSTEP treatment (see **PRECAUTIONS, Allergic Reactions**). Skin discoloration at application sites has been rarely reported.

Probably Causally Related

The following adverse events were reported more frequently in PROSTEP-treated patients than in placebo-treated patients or exhibited a dose response in clinical trials. The reports of awakening at night were collected as one of the expected withdrawal symptoms.

Digestive system—Abdominal pain†
Nervous system—Somnolence*
Skin—Rash,† sweating†

Frequencies for 22 mg/day system
* Reported in 3% to 9% of patients
† Reported in 1% to 3% of patients
Unmarked if reported in <1% of patients

Causal Relationship UNKNOWN

Adverse events reported in PROSTEP and placebo-treated patients at about the same frequency in clinical trials are listed below. The clinical significance of the association between PROSTEP treatment and these events is unknown, but they are reported as alerting information for the clinician.

Body as a Whole—Back pain,† pain*
Digestive system—Constipation,† dyspepsia, nausea†
Musculoskeletal system—Myalgia†
Nervous system—Dizziness,† headache (11%), insomnia*, abnormal dreams‡
Respiratory system—Pharyngitis,* sinusitis*
Urogenital system—Dysmenorrhea†

Frequencies for 22 mg/day system
* Reported in 3% to 9% of patients
† Reported in 1% to 3% of patients
‡ Spontaneous reports only, not seen in clinical trials.
Unmarked if reported in <1% of patients

DRUG ABUSE AND DEPENDENCE

PROSTEP systems are likely to have a low abuse potential based on differences between it and cigarettes in four characteristics commonly considered important in contributing to abuse: much slower absorption, much smaller fluctuations in blood levels, lower blood levels of nicotine, and less frequent use (i.e., once daily).

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Nicotine Delivery Rate *(in vivo)*	Nicotine in System	System Size	Package Size	NDC Number
22 mg/day	30 mg	7.0 cm^2	7 systems	0005-2402-90
11 mg/day	15 mg	3.5 cm^2	7 systems	0005-2401-90

The abuse potential of PROSTEP systems was examined in a prospective, randomized trial of 10 smokers (5 drug abusers and 5 non-abusers). "Liking" scores for either one (22 mg/day) or two systems (44 mg/day) were no different from placebo. No abuse potential was observed in that study.
Dependence on nicotine polacrilex chewing gum replacement therapy has been reported and such dependence might also occur from transference to PROSTEP systems of tobacco-based nicotine dependence. The use of the system beyond 3 months has not been evaluated and should be discouraged.
PROSTEP therapy has been evaluated in both a gradual and abrupt discontinuation of treatment. If gradual withdrawal is desirable, patients using the 22 mg/day PROSTEP treatment should use the 11 mg/day dosage for 2 to 4 weeks (see **Individualization of Dosage** and **DOSAGE AND ADMINISTRATION**).

OVERDOSAGE

The effects of applying several PROSTEP systems simultaneously or of swallowing unused PROSTEP systems are unknown (see **WARNINGS, Safety Note Concerning Children**).
The oral LD_{50} for nicotine in rodents varies with the species but is in excess of 24 mg/kg; death is due to respiratory paralysis. The oral minimum lethal dose of nicotine in dogs is greater than 5 mg/kg. The oral minimum acute lethal dose for nicotine in human adults is reported to be 40 to 60 mg (< 1 mg/kg).
PROSTEP gels containing 8 mg of nicotine were ingested by 12 adult smokers with an average weight of 74 kg (range 62–93 kg). Peak nicotine serum levels were 9.5 ng/mL (range 3–18 ng/mL) and occurred at 2 hours (1–2 hours) and declined to baseline levels by 8 hours after ingestion. Some gastrointestinal effects (burning on ingestion and nausea) were reported.
Signs and symptoms of an overdose of PROSTEP systems would be expected to be the same as those of acute nicotine poisoning including: pallor, cold sweat, nausea, salivation, vomiting, abdominal pain, diarrhea, headache, dizziness, disturbed hearing and vision, tremor, mental confusion, and weakness. Prostration, hypotension, and respiratory failure may ensue with large overdoses. Lethal doses produce convulsions quickly and death follows as a result of peripheral or central respiratory paralysis or, less frequently, cardiac failure.

Overdose from Topical Exposure

The PROSTEP system should be removed immediately if the patient shows signs of overdosage and the patient should seek immediate medical care. The skin surface may be flushed with water and dried. No soap should be used since it may increase nicotine absorption. Nicotine will continue to be delivered into the bloodstream for several hours (see **Pharmacokinetics**) after removal of the system because of a depot of nicotine in the skin.

Overdose from Ingestion

Ingestion of a 22 mg/day PROSTEP system containing 30 mg of nicotine is potentially more harmful than ingestion of a used system which contains about 8 mg after 24 hours use. Persons ingesting PROSTEP systems should be referred to a health care facility for management. Due to the possibility of nicotine-induced seizures, activated charcoal should be administered. In unconscious patients with a secure airway, instill activated charcoal via nasogastric tube. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the system. Repeated doses of activated charcoal should be administered as long as the system remains in the gastrointestinal tract since it will continue to release nicotine for many hours.

Management of Nicotine Poisoning

Other supportive measures include diazepam or barbiturates for seizures, atropine for excessive bronchial secretions or diarrhea, respiratory support for respiratory failure, and vigorous fluid support for hypotension and cardiovascular collapse.

DOSAGE AND ADMINISTRATION

Patients must desire to stop smoking and should be instructed to *stop smoking immediately* as they begin using PROSTEP therapy. The patient should read the patient instruction sheet on PROSTEP treatment and be encouraged to ask any questions. Treatment should be initiated with PROSTEP 22 mg/day except for patients who weigh less than 100 pounds. They may start with PROSTEP 11 mg/day and the dose increased as appropriate (see **Individualization of Dosage**). Once the appropriate dosage is selected the patient should begin 4–8 weeks of therapy at that dosage. The patient should stop smoking cigarettes completely during this period. If the patient is unable to stop cigarette smoking within 4 weeks, PROSTEP should probably be stopped, since few additional patients in clinical trials were able to quit after this time.
Those who have successfully stopped smoking during that time may have PROSTEP therapy discontinued. If a gradual reduction is desired, patients may be treated for an additional 2 to 4 weeks, after which treatment should be terminated.
The entire course of nicotine substitution should take 6–12 weeks. The use of PROSTEP systems beyond 3 months has not been studied and should be discouraged.
The PROSTEP system should be applied promptly upon its removal from the protective pouch to prevent evaporative loss of nicotine from the system. PROSTEP systems should be used only when the pouch is intact to assure that the product has not been tampered with.
PROSTEP systems should be applied only once a day to a non-hairy, clean, and dry skin site on the upper trunk or upper outer arm. After 24 hours, the used PROSTEP system should be removed and a new system applied to an alternate skin site. Skin sites should not be reused for at least a week. Patients should be cautioned not to continue to use the same system for more than 24 hours.

SAFETY AND HANDLING

PROSTEP systems can be a dermal irritant and can cause contact sensitization. Although exposure of health care workers to nicotine from PROSTEP systems should be minimal, care should be taken to avoid unnecessary contact with active systems. If you do handle active systems, wash with water alone, since soap may increase nicotine absorption. Do not touch your eyes.

Disposal

When the used system is removed from the skin, it should be folded over with the adhesive sides together and placed in the protective pouch which contained the new system. The used system should be immediately disposed of in such a way as to prevent its access by children or pets. See patient information for further directions for handling and disposal.

HOW SUPPLIED

[See table above.]

How to Store

Do not store above 25°C (77°F) because PROSTEP systems are sensitive to heat. A slight discoloration of the system is not significant.
Do not store unpouched. Once removed from the protective pouch, PROSTEP systems should be applied promptly since nicotine is volatile and the system may lose strength.
CAUTION: Federal law prohibits dispensing without prescription.

Manufactured for
LEDERLE LABORATORIES DIVISION
Pearl River, New York 10965
by
élan pharma Ltd.
Athlone, County Westmeath
Ireland
Using Elan's DERMAFLEX® transdermal system.
Shown in Product Identification Guide, page 320

PYRAZINAMIDE TABLETS, USP ℞
500 mg

DESCRIPTION

Pyrazinamide, the pyrazine analogue of nicotinamide, is an antituberculous agent. It is a white crystalline powder, stable at room temperature, and sparingly soluble in water. Pyrazinamide has the following chemical formula: $C_5H_5N_3O$, and the following molecular weight: 123.11.
Each Pyrazinamide tablet for oral administration contains 500 mg of pyrazinamide and the following inactive ingredients: corn starch, magnesium stearate, modified food starch and stearic acid.

CLINICAL PHARMACOLOGY

Pyrazinamide is well absorbed from the GI tract and attains peak plasma concentrations within 2 hours. Plasma concentrations generally range from 30 to 50 mcg/mL with doses of 20 to 25 mg/kg. It is widely distributed in body tissues and fluids including the liver, lungs and cerebrospinal fluid (CSF). The CSF concentration is approximately equal to concurrent steady-state plasma concentrations in patients with inflamed meninges.[1] Pyrazinamide is approximately 10% bound to plasma proteins.[2]
The half-life (t1/2) of pyrazinamide is 9 to 10 hours in patients with normal renal and hepatic function. The plasma half-life may be prolonged in patients with impaired renal or hepatic function. Pyrazinamide is hydrolyzed in the liver to its major active metabolite, pyrazinoic acid. Pyrazinoic acid is hydroxylated to the main excretory product, 5-hydroxypyrazinoic acid.[3]
Approximately 70% of an oral dose is excreted in urine, mainly by glomerular filtration within 24 hours.[3]
Pyrazinamide may be bacteriostatic or bactericidal against *Mycobacterium tuberculosis* depending on the concentration of the drug attained at the site of infection. The mechanism of action is unknown. *In vitro* and *in vivo* the drug is active only at a slightly acidic pH.

INDICATIONS AND USAGE

Pyrazinamide is indicated for the initial treatment of active tuberculosis in adults and children when combined with other antituberculous agents. (The current recommendation of the CDC for drug-susceptible disease is to use a six-month regimen for initial treatment of active tuberculosis, consisting of isoniazid, rifampin and pyrazinamide given for 2 months, followed by isoniazid and rifampin for 4 months.*[4])
(Patients with drug-resistant disease should be treated with regimens individualized to their situation. Pyrazinamide frequently will be an important component of such therapy.)
(In patients with concomitant HIV infection, the physician should be aware of current recommendations of CDC. It is possible these patients may require a longer course of treatment.)
It is also indicated after treatment failure with other primary drugs in any form of active tuberculosis.
Pyrazinamide should only be used in conjunction with other effective antituberculous agents.

*See recommendations of Center for Disease Control (CDC) and American Thoracic Society for complete regimen and dosage recommendations.[4]

CONTRAINDICATIONS

Pyrazinamide is contraindicated in persons:
- with severe hepatic damage.
- who have shown hypersensitivity to it.
- with acute gout.

WARNINGS

Patients started on pyrazinamide should have baseline serum uric acid and liver function determinations. Those patients with preexisting liver disease or those at increased risk for drug related hepatitis (e.g., alcohol abusers) should be followed closely.
Pyrazinamide should be discontinued and not be resumed if signs of hepatocellular damage or hyperuricemia accompanied by an acute gouty arthritis appear.

PRECAUTIONS

General: Pyrazinamide inhibits renal excretion of urates, frequently resulting in hyperuricemia which is usually asymptomatic. If hyperuricemia is accompanied by acute gouty arthritis, pyrazinamide should be discontinued.
Pyrazinamide should be used with caution in patients with a history of diabetes mellitus, as management may be more difficult.
Primary resistance of *M. tuberculosis* to pyrazinamide is uncommon. In cases with known or suspected drug resistance, *in vitro* susceptibility tests with recent cultures of *M. tuberculosis* against pyrazinamide and the usual primary drugs should be performed. There are few reliable *in vitro* tests for pyrazinamide resistance. A reference laboratory capable of performing these studies must be employed.
Information for Patients: Patients should be instructed to notify their physicians promptly if they experience any of the following: fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, pain or swelling of the joints.
Compliance with the full course of therapy must be emphasized, and the importance of not missing any doses must be stressed.
Laboratory Tests: Baseline liver function studies [especially ALT (SGPT), AST (SGOT) determinations] and uric acid levels should be determined prior to therapy. Appropriate laboratory testing should be performed at periodic intervals and if any clinical signs or symptoms occur during therapy.
Drug/Laboratory Test Interactions: Pyrazinamide has been reported to interfere with ACETEST® and KETOSTIX® urine tests to produce a pink-brown color.[5]
Carcinogenicity, Mutagenicity, Impairment of Fertility[6,7,8]**:** In lifetime bioassays in rats and mice, pyrazinamide was administered in the diet at concentrations of up to 10,000 ppm. This resulted in estimated daily doses for the mouse of 2 g/kg, or 40 times the maximum human dose, and for the rat of 0.5 g/kg, or 10 times the maximum human dose. Pyrazinamide was not carcinogenic in rats or male mice and no conclusion was possible for female mice due to insufficient numbers of surviving control mice.

ing one (1) or two (2) inhalations of pirbuterol (0.2–0.4 mg). The duration of action of MAXAIR is maintained for 5 hours (the time at which the last observations were made) in a substantial number of patients, based on a 15% or greater increase in FEV_1. In controlled repetitive dose studies of 12 weeks duration, 74% of 156 patients on pirbuterol and 62% of 141 patients on metaproterenol showed a clinically significant improvement based on a 15% or greater increase in FEV_1 on at least half of the days. Onset and duration were equivalent to that seen in single dose studies. Continued effectiveness was demonstrated over the 12-week period in the majority (94%) of responding patients; however, chronic dosing was associated with the development of tachyphylaxis (tolerance) to the bronchodilator effect in some patients in both treatment groups.

A placebo-controlled double-blind single dose study (24 patients per treatment group), utilizing continuous Holter monitoring for 5 hours after drug administration, showed no significant difference in ectopic activity between the placebo control group and MAXAIR at the recommended dose (0.2–0.4 mg), and twice the recommended dose (0.8 mg). As with other inhaled beta adrenergic agonists, supraventricular and ventricular ectopic beats have been seen with MAXAIR (see WARNINGS).

Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

Pharmacokinetics

As expected by extrapolation from oral data, systemic blood levels of pirbuterol are below the limit of assay sensitivity (2–5 ng/ml) following inhalation of doses up to 0.8 mg (twice the maximum recommended dose). A mean of 51% of the dose is recovered in urine as pirbuterol plus its sulfate conjugate following administration by aerosol. Pirbuterol is not metabolized by catechol-O-methyltransferase. The percent of administered dose recovered as pirbuterol plus its sulfate conjugate does not change significantly over the dose range of 0.4 mg to 0.8 mg and is not significantly different from that after oral administration of pirbuterol. The plasma half-life measured after oral administration is about two hours.

INDICATIONS AND USAGE

MAXAIR Inhaler is indicated for the prevention and reversal of bronchospasm in patients with reversible bronchospasm including asthma. It may be used with or without concurrent theophylline and/or steroid therapy.

CONTRAINDICATIONS

MAXAIR is contraindicated in patients with a history of hypersensitivity to any of its ingredients.

WARNINGS

As with other beta adrenergic aerosols, MAXAIR should not be used in excess. Controlled clinical studies and other clinical experience have shown that MAXAIR like other inhaled beta adrenergic agonists can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes. As with other beta adrenergic aerosols, the potential for paradoxical bronchospasm (which can be life threatening) should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

The contents of MAXAIR Inhaler are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperature above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

PRECAUTIONS

General

Since pirbuterol is a sympathomimetic amine, it should be used with caution in patients with cardiovascular disorders, including ischemic heart disease, hypertension, or cardiac arrhythmias, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines or who have convulsive disorders.

Significant changes in systolic and diastolic blood pressure could be expected to occur in some patients after use of any beta adrenergic aerosol bronchodilator.

Information for Patients

MAXAIR effects may last up to five hours or longer. It should not be used more often than recommended and the patient should not increase the number of inhalations or frequency of use without first asking the physician. If symptoms of asthma get worse, adverse reactions occur, or the patient does not respond to the usual dose, the patient should be instructed to contact the physician immediately. The patient should be advised to see the Illustrated Directions for Use.

Drug Interactions

Other beta adrenergic aerosol bronchodilators should not be used concomitantly with MAXAIR because they may have additive effects. Beta adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta adrenergic agonists on the vascular system may be potentiated.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Pirbuterol hydrochloride administered in the diet to rats for 24 months and to mice for 18 months was free of carcinogenic activity at doses corresponding to 200 times the maximum human inhalation dose. In addition, the intragastric intubation of the drug at doses corresponding to 6250 times the maximum recommended human daily inhalation dose resulted in no increase in tumors in a 12-month rat study. Studies with pirbuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Teratogenic Effects—Pregnancy Category C

Reproduction studies have been performed in rats and rabbits by the inhalation route at doses up to 12 times (rat) and 16 times (rabbit) the maximum human inhalation dose and have revealed no significant findings. Animal reproduction studies in rats at *oral doses* up to 300 mg/kg and in rabbits at oral doses up to 100 mg/kg have shown no adverse effect on reproductive behavior, fertility, litter size, peri- and postnatal viability or fetal development. In rabbits at the highest dose level given, 300 mg/kg, abortions and fetal mortality were observed. There are no adequate and well controlled studies in pregnant women and MAXAIR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether MAXAIR is excreted in human milk. Therefore, MAXAIR should be used during nursing only if the potential benefit justifies the possible risk to the newborn.

Pediatric Use

MAXAIR Inhaler is not recommended for patients under the age of 12 years because of insufficient clinical data to establish safety and effectiveness.

ADVERSE REACTIONS

The following rates of adverse reactions to pirbuterol are based on single and multiple dose clinical trials involving 761 patients, 400 of whom received multiple doses (mean duration of treatment was 2.5 months and maximum was 19 months).

The following were the adverse reactions reported more frequently than 1 in 100 patients:

CNS: nervousness (6.9%), tremor (6.0%), headache (2.0%), dizziness (1.2%).
Cardiovascular: palpitations (1.7%), tachycardia (1.2%).
Respiratory: cough (1.2%).
Gastrointestinal: nausea (1.7%).

The following adverse reactions occurred less frequently than 1 in 100 patients and there may be a causal relationship with pirbuterol:

CNS: depression, anxiety, confusion, insomnia, weakness, hyperkinesia, syncope.
Cardiovascular: hypotension, skipped beats, chest pain.
Gastrointestinal: dry mouth, glossitis, abdominal pain/cramps, anorexia, diarrhea, stomatitis, nausea and vomiting.
Ear, Nose and Throat: smell/taste changes, sore throat.
Dermatological: rash, pruritus.
Other: numbness in extremities, alopecia, bruising, fatigue, edema, weight gain, flushing.

Other adverse reactions were reported with a frequency of less than 1 in 100 patients but a causal relationship between pirbuterol and the reaction could not be determined: migraine, productive cough, wheezing, and dermatitis.

The following rates of adverse reactions during three-month controlled clinical trials involving 310 patients are noted. The table does not include mild reactions.

PERCENT OF PATIENTS WITH MODERATE TO SEVERE ADVERSE REACTIONS

Reaction	Pirbuterol N=157	Metaproterenol N=153
Central Nervous System		
tremors	1.3%	3.3%
nervousness	4.5%	2.6%
headache	1.3%	2.0%
weakness	.0%	1.3%
drowsiness	.0%	0.7%
dizziness	0.6%	.0%
Cardiovascular		
palpitations	1.3%	1.3%
tachycardia	1.3%	2.0%
Respiratory		
chest pain/tightness	1.3%	.0%
cough	.0%	0.7%
Gastrointestinal		
nausea	1.3%	2.0%
diarrhea	1.3%	0.7%
dry mouth	1.3%	1.3%
vomiting	.0%	0.7%
Dermatological		
skin reaction	.0%	0.7%
rash	.0%	1.3%
Other		
bruising	0.6%	.0%
smell/taste change	0.6%	.0%
backache	.0%	0.7%
fatigue	.0%	0.7%
hoarseness	.0%	0.7%
nasal congestion	.0%	0.7%

OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-stimulation and/or any of the symptoms listed under adverse reactions, e.g., angina, hypertension or hypotension, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Treatment consists of discontinuation of pirbuterol together with appropriate symptomatic therapy.

The oral acute lethal dose in male and female rats and mice was greater than 2000 mg base/kg. The aerosol acute lethal dose was not determined.

DOSAGE AND ADMINISTRATION

The usual dose for adults and children 12 years and older is two inhalations (0.4 mg) repeated every 4–6 hours. One inhalation (0.2 mg) repeated every 4–6 hours may be sufficient for some patients.

A total daily dose of 12 inhalations should not be exceeded.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

HOW SUPPLIED

MAXAIR Inhaler is supplied in a pressurized aluminum canister with a light-blue plastic actuator and attached white mouthpiece. Each actuation delivers pirbuterol acetate equivalent to 0.2 mg of pirbuterol from the mouthpiece. Net content weight 25.6 g, a minimum of 300 actuations (NDC **0089-0790-21**).

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's).

> **WARNING:** Contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the "Patient's Instructions for Use" of this product pursuant to EPA regulations.

CAUTION

Federal law prohibits dispensing without prescription.

Store between 15° and 30°C (59° to 86°F).

610000 JUNE 1995

Shown in Product Identification Guide, page 322

MEDIHALER-ISO™ ℞

(isoproterenol sulfate)
Inhalation Aerosol

For full prescribing information see leaflet accompanying product or call 800-328-0255 for a copy.

HOW SUPPLIED

MEDIHALER-ISO (isoproterenol sulfate) is an aerosol device which delivers 0.08 mg isoproterenol sulfate through the oral adapter with each depression of the valve.

15-ml and oral adapter containing 21.0 gm, a minimum of 300 actuations (NDC **0089-0785-21**).

15 ml refill vial only, containing 21.0 gm, a minimum of 300 actuations (NDC **0089-0785-11**)

MINITRAN™ ℞

(nitroglycerin)
Transdermal Delivery System

For full prescribing information see leaflet accompanying product or call 800-328-0255 for a copy.

HOW SUPPLIED

[See table at top of next page.]

Continued on next page

3M—Cont.

MINITRAN System Rated Release In Vivo	System Size	Total Nitroglycerin in System	NDC Number (30 per carton)
0.1 mg/hr	3.3 cm^2	9 mg	NDC-0089-0301-02
0.2 mg/hr	6.7 cm^2	18 mg	NDC-0089-0302-02*
0.4 mg/hr	13.3 cm^2	36 mg	NDC-0089-0303-02*
0.6 mg/hr	20.0 cm^2	54 mg	NDC-0089-0304-02

*MINITRAN Transdermal Delivery System, 0.2 mg/hr, 0.4 mg/hr, is also available in cartons of 90 patches bearing NDC-0089-0302-09 and NDC-0089-0303-09 respectively.

NORFLEX™ ℞

(orphenadrine citrate)
Tablets and Injection

PRODUCT OVERVIEW

KEY FACTS

Norflex extended-release tablets provide 12 hours relief from the pain of muscle spasm. Also available in injectable form, IV or IM, also given every 12 hours.

MAJOR USES

Norflex is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with painful musculoskeletal disorders.

SAFETY INFORMATION

Contraindicated in patients with glaucoma, pyloric or duodenal obstruction, stenosing peptic ulcers, prostatic hypertrophy or obstruction of the bladder neck, cardiospasm (megaesophagus) and myasthenia gravis. Contraindicated in patients who have a previous sensitivity to the drug.

PRESCRIBING INFORMATION

NORFLEX™ ℞

(orphenadrine citrate)
Tablets and Injection

DESCRIPTION

Orphenadrine citrate is the citrate salt of orphenadrine (2-dimethylaminoethyl 2-methylbenzhydryl ether citrate). It occurs as a white, crystalline powder having a bitter taste. It is practically odorless; sparingly soluble in water, slightly soluble in alcohol.

Each Norflex Tablet contains 100 mg orphenadrine citrate. Norflex Tablets also contain: calcium stearate, ethylcellulose, and lactose. Norflex Injection contains 60 mg of orphenadrine citrate in aqueous solution in each ampul. Norflex Injection also contains: sodium bisulfite NF, 2.0 mg; sodium chloride USP, 5.8 mg; sodium hydroxide, to adjust pH; and water for injection USP, q.s. to 2 mL.

ACTIONS

The mode of therapeutic action has not been clearly identified, but may be related to its analgesic properties. Orphenadrine citrate also possesses anticholinergic actions.

INDICATIONS

Orphenadrine citrate is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute painful musculoskeletal conditions. The mode of action of the drug has not been clearly identified, but may be related to its analgesic properties. Orphenadrine citrate does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Contraindicated in patients with glaucoma, pyloric or duodenal obstruction, stenosing peptic ulcers, prostatic hypertrophy or obstruction of the bladder neck, cardio-spasm (megaesophagus) and myasthenia gravis. Contraindicated in patients who have demonstrated a previous hypersensitivity to the drug.

WARNINGS

Some patients may experience transient episodes of light-headedness, dizziness or syncope. Norflex may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; ambulatory patients should therefore be cautioned accordingly.

Norflex Injection contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than nonasthmatic people.

PREGNANCY

Pregnancy Category C. Animal reproduction studies have not been conducted with Norflex. It is also not known whether Norflex can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norflex should be given to a pregnant woman only if clearly needed.

USAGE IN CHILDREN

Safety and effectiveness in children have not been established; therefore, this drug is not recommended for use in the pediatric age group.

PRECAUTIONS

Confusion, anxiety and tremors have been reported in a few patients receiving propoxyphene and orphenadrine concomitantly. As these symptoms may be simply due to an additive effect, reduction of dosage and/or discontinuation of one or both agents is recommended in such cases.

Orphenadrine citrate should be used with caution in patients with tachycardia, cardiac decompensation, coronary insufficiency, cardiac arrhythmias.

Safety of continuous long-term therapy with orphenadrine has not been established. Therefore, if orphenadrine is prescribed for prolonged use, periodic monitoring of blood, urine and liver function values is recommended.

ADVERSE REACTIONS

Adverse reactions of orphenadrine are mainly due to the mild anticholinergic action of orphenadrine, and are usually associated with higher dosage. Dryness of the mouth is usually the first adverse effect to appear. When the daily dose is increased, possible adverse effects include: tachycardia, palpitation, urinary hesitancy or retention, blurred vision, dilatation of pupils, increased ocular tension, weakness, nausea, vomiting, headache, dizziness, constipation, drowsiness, hypersensitivity reactions, pruritus, hallucinations, agitation, tremor, gastric irritation, and rarely urticaria and other dermatoses. Infrequently, an elderly patient may experience some degree of mental confusion. These adverse reactions can usually be eliminated by reduction in dosage. Very rare cases of aplastic anemia associated with the use of orphenadrine tablets have been reported. No causal relationship has been established.

Rare instances of anaphylactic reaction have been reported associated with the intramuscular injection of Norflex Injection.

DOSAGE AND ADMINISTRATION

TABLETS: Adults—Two tablets per day; one in the morning and one in the evening.

INJECTION: Adults—One 2 mL ampul (60 mg) intravenously or intramuscularly; may be repeated every 12 hours. Relief may be maintained by 1 Norflex tablet twice daily.

HOW SUPPLIED

TABLETS: Each round, white tablet imprinted with "3M" on one side and "221" on the other. Bottles of 100 (NDC **0089-0221-10**) and 500 (NDC **0089-0221-50**). Each tablet contains 100 mg of orphenadrine citrate.

INJECTION: Boxes of 6 (NDC **0089-0540-06**) 2 mL ampuls, each ampul containing 60 mg of orphenadrine citrate in aqueous solution.

A.H.F.S. Category 12:08

Store at controlled room temperature, 15°–30°C (59°–86°F).

CAUTION

Federal law prohibits dispensing without prescription.

NRF-16 SEPTEMBER 1993

Shown in Product Identification Guide, page 322

NORGESIC™ ℞
and
NORGESIC™ FORTE ℞

Tablets

ACTIONS

Orphenadrine citrate is a centrally acting (brain stem) compound which in animals selectively blocks facilitatory functions of the reticular formation. Orphenadrine does not produce myoneural block, nor does it affect crossed extensor reflexes. Orphenadrine prevents nicotine-induced convulsions but not those produced by strychnine.

Chronic administration of Norgesic to dogs and rats has revealed no drug-related toxicity. No blood or urine changes were observed, nor were there any macroscopic or microscopic pathological changes detected. Extensive experience with combinations containing aspirin and caffeine has established them as safe agents. The addition of orphenadrine citrate does not alter the toxicity of aspirin and caffeine.

The mode of therapeutic action of orphenadrine has not been clearly identified, but may be related to its analgesic properties. Orphenadrine citrate also possesses anticholinergic actions.

INDICATIONS

1. Symptomatic relief of mild to moderate pain of acute musculoskeletal disorders.
2. The orphenadrine component is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute painful musculoskeletal conditions.

The mode of action of orphenadrine has not been clearly identified, but may be related to its analgesic properties. Norgesic and Norgesic Forte do not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Because of the mild anticholinergic effect of orphenadrine, Norgesic or Norgesic Forte should not be used in patients with glaucoma, pyloric or duodenal obstruction, achalasia, prostatic hypertrophy or obstructions at the bladder neck. Norgesic or Norgesic Forte is also contraindicated in patients with myasthenia gravis and in patients known to be sensitive to aspirin or caffeine.

The drug is contraindicated in patients who have demonstrated a previous hypersensitivity to the drug.

WARNINGS

Reye Syndrome may develop in individuals who have chicken pox, influenza, or flu symptoms. Some studies suggest possible association between the development of Reye Syndrome and the use of medicines containing salicylate or aspirin. Norgesic and Norgesic Forte contain aspirin and therefore are not recommended for use in patients with chicken pox, influenza, or flu symptoms.

Norgesic Forte may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; ambulatory patients should therefore be cautioned accordingly.

Aspirin should be used with extreme caution in the presence of peptic ulcers and coagulation abnormalities.

USAGE IN PREGNANCY

Since safety of the use of this preparation in pregnancy, during lactation, or in the childbearing age has not been established, use of the drug in such patients requires that the potential benefits of the drug be weighed against its possible hazard to the mother and child.

USAGE IN CHILDREN

The safe and effective use of this drug in children has not been established. Usage of this drug in children under 12 years of age is not recommended.

PRECAUTIONS

Confusion, anxiety and tremors have been reported in a few patients receiving propoxyphene and orphenadrine concomitantly. As these symptoms may be simply due to an additive effect, reduction of dosage and/or discontinuation of one or both agents is recommended in such cases.

Safety of continuous long term therapy with Norgesic Forte has not been established; therefore, if Norgesic Forte is prescribed for prolonged use, periodic monitoring of blood, urine and liver function values is recommended.

ADVERSE REACTIONS

Side effects of Norgesic or Norgesic Forte are those seen with aspirin and caffeine or those usually associated with mild anticholinergic agents. These may include tachycardia, palpitation, urinary hesitancy or retention, dry mouth, blurred vision, dilatation of the pupil, increased intraocular tension, weakness, nausea, vomiting, headache, dizziness, constipation, drowsiness, and rarely, urticaria and other dermatoses. Infrequently, an elderly patient may experience some degree of confusion. Mild central excitation and occasional hallucinations may be observed. These mild side effects can usually be eliminated by reduction in dosage. One case of aplastic anemia associated with the use of Norgesic has been reported. No causal relationship has been established. Rare G.I. hemorrhage due to aspirin content may be associated with the administration of Norgesic or Norgesic Forte. Some patients may experience transient episodes of light-headedness, dizziness or syncope.

DOSAGE AND ADMINISTRATION

Norgesic: Adults 1 to 2 tablets 3 to 4 times daily.

Norgesic Forte: Adults ½ to 1 tablet 3 to 4 times daily.

HOW SUPPLIED

Norgesic tablets can be identified by their three layers colored light green, white and yellow. Each round tablet is embossed "NORGESIC" on one side and "3M" on the other and contains orphenadrine citrate (2-dimethylaminoethyl 2-methylbenzhydryl ether citrate) 25 mg, aspirin 385 mg, and caffeine 30 mg.

Norgesic Forte tablets are exactly twice the strength of Norgesic. They are identified by their scored capsule shape and by their three layers colored light green, white and yellow. Each capsule shaped tablet is embossed "NORGESIC FORTE" on one side and "3M" on the other and contains

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tion, refer to the acetylcysteine package insert. Do not await the results of assays for acetaminophen level before initiating treatment with acetylcysteine. The following additional procedures are recommended: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. A plasma acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

Serious toxicity or fatalities are extremely infrequent in children, possibly due to differences in the way they metabolize acetaminophen. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount was ingested, obtain an plasma acetaminophen level. The acetaminophen plasma level should be obtained as soon as possible, but no sooner than 4 hours following the ingestion. Induce emesis using syrup of ipecac. If the plasma level is obtained and falls above the broken line on the acetaminophen overdose nomogram, the acetylcysteine therapy should be initiated and continued for a full course of therapy. If acetaminophen plasma assay capability is not available, and the estimated acetaminophen ingestion exceeds 150 mg/kg, acetylcysteine therapy should be initiated and continued for a full course of therapy.

For additional emergency information, call your regional poison center or call the Rocky Mountain Poison Center toll-free, (1-800-525-6115).

Chlorpheniramine toxicity should be treated as you would an antihistamine/anticholinergic overdose and is likely to be present within a few hours after acute ingestion.

Symptoms from pseudoephedrine overdose consist most often of mild anxiety, tachycardia and/or mild hypertension. Symptoms usually appear within 4 to 8 hours of ingestion and are transient, usually requiring no treatment.

INACTIVE INGREDIENTS

Chewable Tablets: Aspartame, Basic Polymuthacrylate, cellulose acetate, citric acid, flavors, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, Blue #1, Red #7.

Liquid: Benzoic acid, citric acid, flavors, glycerin, malic acid, polyethylene glycol, propylene glycol, sodium benzoate, sorbitol, sucrose, purified water, Blue #1 and Red #40.

HOW SUPPLIED

Chewable Tablets (colored purple, scored, imprinted "Tylenol Cold") on one side and "TC" on opposite side—bottles of 24. **Liquid Formula**—bottles (colored purple) of 4 fl. oz.

Shown in Product Identification Guide, page 322

CHILDREN'S TYLENOL® OTC
COLD Multi Symptom
PLUS COUGH
Chewable Tablets and Liquid

DESCRIPTION

Each ***CHILDREN'S TYLENOL® COLD Multi Symptom Plus Cough Chewable Cherry-Flavored Tablet*** contains:

acetaminophen 80 mg
chlorpheniramine maleate 0.5 mg
dextromethorphan hydrobromide 2.5 mg
pseudoephedrine hydrochloride 7.5 mg

CHILDREN'S TYLENOL® COLD Multi Symptom Plus Cough Liquid is cherry flavored and contains no alcohol. Each teaspoon (5 ml) contains acetaminophen 160 mg, chlorpheniramine maleate 1 mg, dextromethorphan hydrobromide 5 mg and pseudoephedrine hydrochloride 15 mg.

ACTIONS

CHILDREN'S TYLENOL® COLD Multi Symptom Plus Cough Chewable Tablets and ***Liquid*** combines the analgesic-antipyretic acetaminophen with the decongestant pseudoephedrine hydrochloride, the cough suppressant dextromethorphan hydrobromide, and the antihistamine chlorpheniramine maleate to help relieve coughs, nasal congestion, and sore throat, dry runny noses, and prevent sneezing as well as to relieve the fever, aches, pains and general discomfort associated with colds and upper respiratory infections.

Acetaminophen is equal to aspirin in analgesic and antipyretic effectiveness and it is unlikely to produce the side effects often associated with aspirin or aspirin-containing products.

INDICATIONS

For temporary relief of coughs, nasal congestion, runny nose, sore throat, sneezing, minor aches and pains, headaches and fever due to the common cold, hay fever or other upper respiratory allergies.

PRECAUTION

If a rare sensitivity reaction occurs, the drug should be stopped.

DIRECTIONS

All doses may be repeated every 4–6 hours, not to exceed 4 doses in 24 hours.

Administer to children under 6 years only on the advice of a physician.

CHILDREN'S TYLENOL® COLD Plus Cough Chewable Tablets: 2–5 years—2 tablets, 6–11 years—4 tablets.

CHILDREN'S TYLENOL® COLD Plus Cough Liquid Formula: 2–5 years—1 teaspoonful, 6–11 years—2 teaspoonfuls. Measuring cup is provided and marked for accurate dosing.

WARNING

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. IN CASE OF ACCIDENTAL OVERDOSE, CONTACT A DOCTOR OR POISON CONTROL CENTER IMMEDIATELY. PROMPT MEDICAL ATTENTION IS CRITICAL EVEN IF YOU DO NOT NOTICE ANY SIGNS OR SYMPTOMS. DO NOT USE WITH OTHER PRODUCTS CONTAINING ACETAMINOPHEN. DO NOT EXCEED RECOMMENDED DOSAGE. Do not take for pain for more than 5 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists for gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea or vomiting, consult a doctor promptly. If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor. May cause excitability especially in children. Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, heart disease, high blood pressure, thyroid disease, or diabetes, without first consulting the child's doctor. May cause drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor. A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash or persistent headache, consult a doctor. Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor.

NOTE: In addition to the above:

Chewable Tablets—DO NOT USE IF CARTON IS OPENED, OR IF PRINTED NECK WRAP OR PRINTED FOIL INNER SEAL IS BROKEN. PHENYLKETONURICS: CONTAINS PHENYLALANINE 4 MG PER TABLET.

Liquid—DO NOT USE IF CARTON IS OPENED, OR IF PRINTED PLASTIC BOTTLE WRAP OR PRINTED FOIL INNER SEAL IS BROKEN.

DRUG INTERACTION PRECAUTION

Do not give this product to a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your child's prescription drug contains an MAOI, consult a health professional before giving this product.

OVERDOSAGE INFORMATION

Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In adults and adolescents, hepatic toxicity has rarely been reported following ingestion of acute overdoses of less than 10 grams. Fatalities are infrequent (less than 3–4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children, an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion.

In adults and adolescents, regardless of the quantity of acetaminophen reported to have been ingested, administer acetylcysteine immediately if 24 hours or less have elapsed from the reported time of ingestion. For full prescribing information, refer to the acetylcysteine package insert. Do not await the results of assays for plasma acetaminophen level before initiating treatment with acetylcysteine. The following additional procedures are recommended: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. A plasma acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, acetylcysteine therapy should be continued. Liver function studies should be obtained initially and repeated at 24-hour intervals.

Serious toxicity or fatalities are extremely infrequent in children, possibly due to differences in the way they metabolize acetaminophen. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount was ingested, obtain an plasma acetaminophen level. The plasma acetaminophen level should be obtained as soon as possible, but no sooner than 4 hours following the ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, the acetylcysteine therapy should be initiated and continued for a full course of therapy. If plasma acetaminophen assay capability is not available, and the estimated acetaminophen ingestion exceeds 150 mg/kg, acetylcysteine therapy should be initiated and continued for a full course of therapy.

For additional emergency information, call your regional poison center or call the Rocky Mountain Poison Center toll-free, (1-800-525-6115).

Chlorpheniramine toxicity should be treated as you would an antihistamine/anticholinergic overdose and is likely to be present within a few hours after acute ingestion.

Symptoms from pseudoephedrine overdose consist most often of mild anxiety, tachycardia and/or mild hypertension. Symptoms usually appear within 4 to 8 hours of ingestion and are transient, usually requiring no treatment.

Acute dextromethorphan overdose usually does not result in serious signs and symptoms unless massive amounts have been ingested. Signs and symptoms of a substantial overdose may include nausea and vomiting, visual disturbances, CNS disturbances, and urinary retention.

INACTIVE INGREDIENTS

Chewable Tablets: Aspartame, Basic Polymethacrylate, Cellulose Acetate, Colloidal Silicon Dioxide, Flavors, Hydroxypropyl Methylcellulose, Mannitol, Microcrystalline Cellulose, Stearic Acid and Red #7.

Liquid: Citric Acid, Corn Syrup, Flavors, Polyethylene Glycol, Propylene Glycol, Sodium Benzoate, Sodium Carboxymethylcellulose, Sorbitol, Purified Water, Red #33 and Red #40.

HOW SUPPLIED

Chewable Tablets (colored pink, imprinted "TYLENOL C/C" on one side and "TC/C" on the opposite side)—bottles of 24.

Liquid Formula—(red colored) bottles of 4 fl. oz.

Shown in Product Identification Guide, page 323

Children's OTC
TYLENOL® FLU Suspension Liquid

DESCRIPTION

CHILDREN'S TYLENOL® FLU Suspension Liquid is bubblegum flavored and contains no alcohol or aspirin. Each teaspoon (5 mL) contains acetaminophen 160 mg, pseudoephedrine HCl 15 mg, dextromethorphan HBr 7.5 mg, and chlorpheniramine maleate 1 mg.

ACTIONS

CHILDREN'S TYLENOL® FLU Suspension Liquid combines the analgesic-antipyretic acetaminophen with the decongestant pseudoephedrine hydrochloride, the cough suppressant dextromethorphan hydrobromide and the antihistamine chlorpheniramine maleate to help relieve coughs, nasal congestion, and sore throat, dry runny noses, and prevent sneezing as well as to relieve the fever, aches, pains, and general discomfort associated with colds and upper respiratory infections.

Acetaminophen is equal to aspirin in analgesic and antipyretic effectiveness and it is unlikely to produce the side effects often associated with aspirin or aspirin-containing products.

INDICATIONS

Provides fast, effective, temporary relief of fever, minor aches and pains, headaches, sore throat, nasal congestion, runny nose and coughs due to a cold or "flu".

DOSAGE INSTRUCTIONS

Shake well before using. An Accudose™ measuring cup is provided for accurate dosing of ***CHILDREN'S TYLENOL® FLU Suspension Liquid.*** 6–11 years (48–95 lbs): 2 tsp. Administer to children under 6 years only on advice of a physician. All doses may be repeated every 6–8 hours. Not to exceed 4 doses in 24 hours.

WARNING

DO NOT USE IF PRINTED CARTON OVERWRAP IS BROKEN OR MISSING OR IF CARTON IS OPENED. DO NOT USE IF PRINTED PLASTIC "SAFETY SEAL" OR PRINTED FOIL INNER SEAL IS BROKEN. KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN. IN CASE OF ACCIDENTAL OVERDOSE, CONTACT DOCTOR OR POISON CONTROL CENTER IMMEDIATELY. PROMPT MEDICAL ATTENTION IS CRITICAL FOR ADULTS AS WELL AS CHILDREN EVEN IF YOU DO NOT NOTICE ANY SIGNS OR SYMPTOMS. DO NOT USE WITH OTHER PRODUCTS CONTAINING ACETAMINOPHEN. DO NOT EXCEED RECOMMENDED DOSAGE. Do not take for pain for more than 5 days or for fever for more than 3 days unless directed by a doctor. If pain of fever persists, or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. If sore throat is severe, persists for more than 2 days, is accom-

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Anxiety, irritability, restlessness and tobacco cravings occurred about equally in both groups, while other symptoms tended to be slightly more common on placebo spray.

Effects of the Spray

NICOTROL NS and the pepper-containing placebo were both associated with irritant side effects on the nasopharyngeal and ocular tissues. During the first 2 days of treatment, nasal irritation was reported by nearly all (94%) of the patients, the majority of whom rated it as either moderate or severe. Both the frequency and severity of nasal irritation declined with continued use of NICOTROL NS but was still experienced by most (81%) of the patients after 3 weeks of treatment, with most patients rating it as moderate or mild.

Other common side-effects for both active and placebo groups were runny nose, throat irritation, watering eyes, sneezing, and cough.

The following local events were reported somewhat more commonly for active than for placebo spray: nasal congestion, subjective comments related to the taste or use of the dosage form, sinus irritation, transient epistaxis, eye irritation, transient changes in sense of smell, pharyngitis, paraethesias of the nose, mouth or head, numbness of the nose, or mouth, burning of the nose or eyes, earache, facial flushing, transient changes in sense of taste, hoarseness, nasal ulcer or blister.

Effects of Nicotine

Feelings of dependence on the spray were reported by more patients on active spray than placebo. Drug-like effects such as calming were also more frequent on active spray. (See **DRUG ABUSE AND DEPENDENCE**)

Other Adverse Effects

Adverse events which could not be classified and listed above and which were reported by > 1% of patients on active spray are listed in the following table

Adverse Events Not Attributable to Intercurrent Illness

Adverse Event	Active	Placebo
HEADACHE	18%	15%
BACK PAIN	6%	4%
DYSPNEA	5%	6%
NAUSEA	5%	5%
ARTHRALGIA	5%	1%
MENSTRUAL DISORDER	4%	4%
PALPITATION	4%	4%
FLATULENCE	4%	3%
TOOTH DISORDER	4%	1%
GUM PROBLEMS	4%	1%
MYALGIA	3%	4%
ABDOMINAL PAIN	3%	3%
CONFUSION	3%	3%
ACNE	3%	1%
DYSMENORRHEA	3%	0%
PRURITUS	2%	3%

Adverse events reported with a frequency of < 1% among active spray users are listed below:

Body as a Whole: edema peripheral, pain, numbness, allergy

Gastrointestinal: dry mouth, hiccup, diarrhea

Hematologic: purpura

Neurological: aphasia, amnesia, migraine, numbness

Respiratory: bronchitis, bronchospasm, sputum increased

Skin and appendages: rash, purpura

Special Senses: vision abnormal

DRUG ABUSE AND DEPENDENCE

NICOTROL NS has a dependence potential intermediate between other nicotine-based therapies and cigarettes. This is the result of differences between cigarettes, NICOTROL NS, nicotine gum and nicotine patches in pharmacokinetic and dosing characteristics commonly associated with abuse and dependence. NICOTROL NS is distinct from other nicotine-based smoking cessation therapies in its greater speed of onset, greater capacity for self-titration of dose, and frequent and rapid fluctuations in plasma nicotine concentration.

Dependence on nicotine nasal spray occurred in the clinical trials. Feelings of dependency on the spray were reported by 32% of active spray users and 13% of placebo spray users. Such dependence may represent transference of tobacco-related nicotine dependence to NICOTROL NS.

Fifteen to 20% of patients used the active spray for longer periods than recommended (6 months to 1 year) and 5% used the spray at a higher dose than recommended. Some of these patients experienced anxiety about stopping the spray and some reported craving for the spray rather than for cigarettes.

OVERDOSAGE

The oral LD_{50} for nicotine is > 5 mg/kg in dogs and > 24 mg/kg in rodents. Deaths is due to respiratory paralysis. The oral minimum acute lethal dose for nicotine in adult humans is reported to be 40 to 60 mg (< 1 mg/kg). A full bottle of NICOTROL NS contains 100 mg of nicotine.

NICOTROL NS would be expected to be irritating if sprayed in the eyes, mouth or ears. Eye exposure should be treated with copious irrigation with water for 20 minutes. Large oral nicotine ingestions cause vomiting, and the consequences of an overdose will vary; should this occur, patients should contact their physician immediately. For additional emergency information, call your regional poison center or call the National Capital Poison Center toll-free (1-800-498-8666).

Signs and Symptoms of Nicotine Toxicity

Signs and symptoms of an overdose of NICOTROL NS would be expected to be the same as those of acute nicotine poisoning including: pallor, cold sweat, nausea, salivation, vomiting, abdominal pain, diarrhea, headache, dizziness, disturbed hearing and vision, tremor, mental confusion, and weakness. Prostration, hypotension, and respiratory failure may ensue with large overdoses. Lethal doses produce convulsions quickly and death follows as a result of peripheral or central respiratory paralysis or, less frequently, cardiac failure.

Overdose from Ingestion

If emesis has not occurred, it should be induced in conscious patients with a suitable emetic followed by an appropriate dose of activated charcoal. In unconscious patients with a secure airway, instill activated charcoal via a nasogastric tube. A saline cathartic or sorbitol may be added to the first dose of activated charcoal.

Management of Nicotine Poisoning

Other supportive measures include diazepam or barbiturates for seizures, atropine for excessive bronchial secretions or diarrhea, respiratory support for respiratory failure, and vigorous fluid support for hypotension and cardiovascular collapse.

DOSAGE AND ADMINISTRATION

It is important that patients understand the instructions for use of NICOTROL NS, and have their questions answered. They should clearly understand the directions for using NICOTROL NS and safely disposing of the used container. They should be instructed to stop smoking completely when they begin using the product.

Patients should be instructed not to sniff, swallow or inhale through the nose as the spray is being administered. They should also be advised to administer the spray with the head tilted back slightly.

The dose of NICOTROL NS, should be **individualized** on the basis of each patient's nicotine dependence and the occurrence of symptoms of nicotine excess (See Individualization of Dosage).

Each actuation of NICOTROL NS delivers a metered 50 microliter spray containing 0.5 mg of nicotine. One dose is 1 mg of nicotine (2 sprays, one in each nostril).

Patients should be started with 1 or 2 doses per hour, which may be increased up to a maximum recommended dose of 40 mg (80 sprays, somewhat less than $^1/_2$ bottle) per day). For best results, patients should be encouraged to use at least the recommended minimum of 8 doses per day, as less is unlikely to be effective. In clinicals trials, the patients who successfully quit smoking used the product heavily when nicotine withdrawal was at its peak, sometimes up to the recommended maximum of 40 doses per day (in heavier smokers).

Dosing recommendations are summarized in Table 4. [See table below.]

No tapering strategy has been shown to be optimal in clinical studies. Many patients simply stopped using the spray at their last clinic visit.

Recommended strategies for discontinuation of use include suggesting that patients: use only $^1/_2$ a dose (1 spray) at a time, use the spray less frequently, keep a tally of daily usage, try to meet a steadily reducing usage target, skip a dose by not medicating every hour, or set a planned "quit date" for stopping use of the spray.

Individualization of Dosage

The success or failure of smoking cessation is influenced by the quality, intensity and frequency of supportive care. Patients are more likely to quit smoking if they are seen frequently and participate in formal smoking cessation programs.

Table 4

Maximum Recommended Duration of Treatment	Recommended Doses per Hour	Maximum Doses per Hour	Maximum Doses per Day
3 months	1–2*	5	40

* One dose = 2 sprays (one in each nostril). One dose delivers 1 mg of nicotine to the nasal mucosa.

The goal of NICOTROL NS therapy is complete abstinence. If a patient is unable to stop smoking by the fourth week of therapy, treatment should probably be discontinued.

Patients who fail to quit on any attempt may benefit from interventions to improve their chances for success on subsequent attempts. Patients who were unsuccessful should be counseled and should then probably be given a "therapy holiday" before the next attempt. A new quit attempt should be encouraged when conditions are more favorable.

Based on the clinical trials, a reasonable approach to assisting patients in their attempt to quit smoking is to begin initial treatment, using the recommended dosage (See **DOSAGE AND ADMINISTRATION**). Regular use of the spray during the first week of treatment may help patients adapt to the irritant effects of the spray. Dosage can then be adjusted in those subjects with signs or symptoms of nicotine withdrawal or excess. Patients who are successfully abstinent on NICOTROL NS should be treated at the selected dosage for up to 8 weeks, following which use of the spray should be discontinued over the next 4 to 6 weeks. Some patients may not require gradual reduction of dosage and may abruptly stop treatment successfully. Treatment with NICOTROL NS for longer periods has not been shown to improve outcome, and the safety of use for periods longer than 6 months has not been established.

The symptoms of nicotine withdrawal overlap those of nicotine excess (See **Pharmacodynamics and ADVERSE REACTIONS** sections). Since patients using NICOTROL NS may also smoke intermittently, it is sometimes difficult to determine if patients are experiencing nicotine withdrawal or nicotine excess. Controlled clinical trials of nicotine products suggest that palpitations, nausea and sweating are more often symptoms of nicotine excess, whereas anxiety, nervousness and irritability are more often symptoms of nicotine withdrawal

SAFETY AND HANDLING

As with all medicines, especially ones in liquid form, care should be taken in handling NICOTROL NS during periods of opening and closing the container (See **WARNINGS and Safety Note Concerning Children**). If it is dropped it may break. If this occurs, the spill should be cleaned up immediately with an absorbent cloth/paper towel. Care should be taken to avoid contact of the solution with the skin. Broken glass should be picked up carefully, using a broom. The area of the spill should be washed several times. Absorbent material may be disposed of as any other household waste. Should even a small amount of NICOTROL NS come in contact with the skin, lips, mouth, eyes or ears, the affected area(s) should be immediately rinsed with water only.

Disposal

Used bottles of NICOTROL NS should be disposed of with their child-resistant caps in place. Used bottles should be disposed of in such a way as to prevent access by children or pets. See patient information for further information on handling and disposal.

HOW SUPPLIED

NDC 0045-0899-01

Nicotrol®NS (nicotine nasal spray) 10 mg/mL, is supplied in individual 10 mL bottles.

Each unit consists of a glass container, mounted with a metered spray pump

A patient information leaflet is enclosed with the package

Store at room temperature not to exceed 30°C/86°F.

CAUTION: Federal law prohibits dispensing without prescription.

Shown in Product Identification Section, page 322

NICOTROL® OTC
NICOTINE TRANSDERMAL SYSTEM

DESCRIPTION

NICOTROL® (nicotine transdermal system) is a multilayered, rectangular, thin film laminated unit containing nicotine as the active ingredient. ***NICOTROL®*** Patch provides systemic delivery of 15 mg of nicotine over 16 hours.

ACTIONS

NICOTROL® (nicotine transdermal system) Patch helps smokers quit by reducing nicotine withdrawal symptoms. Many ***NICOTROL®*** Patch users will be able to stop smoking for a few days but often will start smoking again. Most smokers have to try to quit several times before they completely stop.

Your own chances of quitting smoking depend on how much you want to quit, how strongly you are addicted to nicotine and how closely you follow a quitting program like the PATHWAYS TO CHANGE® Program that comes with the ***NICOTROL®*** Patch.

If you find you cannot stop or if you start smoking again after using ***NICOTROL®*** Patch, please talk to a health care professional who can help you find a program that may work better for you. Remember that breaking this addiction doesn't happen overnight.

Because the ***NICOTROL®*** Patch provides some nicotine, the ***NICOTROL®*** Patch will help you stop smoking by reducing nicotine withdrawal symptoms such as nicotine cravings, nervousness and irritability.

INDICATIONS

NICOTROL® Patch is indicated as a stop smoking aid to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking.

DIRECTIONS

- Stop smoking completely when you begin using the ***NICOTROL®*** Patch.
- Refer to enclosed patient information leaflet before using this product.
- Use one ***NICOTROL®*** Patch every day for six weeks. Remove backing from the patch and immediately press onto clean dry hairless skin. Hold for ten seconds. Wash hands.
- The ***NICOTROL®*** Patch should be worn during awake hours and removed prior to sleep.

FOR BEST RESULTS IN QUITTING SMOKING

1. Firmly commit to quitting smoking.
2. Use enclosed support materials.
3. Use the ***NICOTROL®*** Patches for six weeks.
4. Stop using ***NICOTROL®*** Patches at the end of week six. If you still feel the need for ***NICOTROL®*** Patches talk to your doctor.

WARNINGS

- Keep this and all medication out of reach of children and pets. Even used patches have enough nicotine to poison children and pets. Be sure to fold sticky ends together and throw away out of reach of children and pets. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.
- Nicotine can increase your baby's heart rate. First try to stop smoking without the nicotine patch. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.
- Do not smoke even when you are not wearing the patch. The nicotine in your skin will still be entering your bloodstream for several hours after you take the patch off.
- If you forget to remove the patch at bedtime you may have vivid dreams or other sleep disruptions.

Do Not Use if You:

- Continue to smoke, chew tobacco, use snuff, or use a nicotine gum or other nicotine containing products.

Ask Your Doctor Before Use if You:

- Are under 18 years of age.
- Have heart disease, recent heart attack or irregular heartbeat. Nicotine can increase your heart rate.
- Have high blood pressure not controlled with medication. Nicotine can increase blood pressure.
- Take prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.
- Are allergic to adhesive tape or have skin problems, because you are more likely to get rashes.

Stop Use and See Your Doctor if You Have:

- Skin redness caused by the patch that does not go away after four days, or if your skin swells or you get a rash.
- Irregular heartbeat or palpitations.
- Symptoms of nicotine overdose such as nausea, vomiting, dizziness, weakness and rapid heartbeat.

INACTIVE INGREDIENTS

Polyisobutylenes, polybutene non-woven polyester, pigmented aluminized and clear polyesters.

HOW SUPPLIED

Starter Kit-7 patches, Refill Kit-7 and 14 patches. DO NOT USE IF POUCH IS DAMAGED OR OPEN. Do not Store above 86°F (30°C)

- **Not for sale to those under 18 years of age**
- **Proof of age required.**
- **Not for sale in vending machines or from any source where proof of age cannot be verified.**

Shown in Product Identification Guide, page 322

PEDIACARE® Cough-Cold Liquid and Chewable Tablets **OTC**
PEDIACARE® NightRest Cough-Cold Liquid
PEDIACARE® Infants' Drops Decongestant
PEDIACARE® Infants' Drops Decongestant Plus Cough

DESCRIPTION

Each 5 ml of ***PEDIACARE® Cough-Cold Liquid*** contains pseudoephedrine hydrochloride 15 mg, chlorpheniramine maleate 1 mg and dextromethorphan hydrobromide 5 mg. Each ***PEDIACARE® Cough-Cold Chewable Tablet*** contains pseudoephedrine hydrochloride 15 mg, chlorpheniramine maleate 1 mg and dextromethorphan hydrobromide 5 mg. Each 0.8 ml oral dropper of ***PEDIACARE® Infants' Drops Decongestant*** contains pseudoephedrine hydrochloride 7.5 mg. Each 0.8 oral dropper of ***PEDIACARE® Infants' Drops Decongestant Plus Cough*** contains pseudoephedrine hydrochloride 7.5 mg and dextromethorphan hydrobromide 2.5 mg. ***PEDIACARE® NightRest Cough-Cold Liquid*** contains pseudoephedrine hydrochloride 15 mg, chlorpheniramine maleate 1 mg and dextromethorphan hydrobromide 7.5 mg per 5 ml. ***PEDIACARE® Cough-Cold Liquid*** and ***NightRest Cough-Cold Liquid*** are stable, cherry flavored and red in color. ***PEDIACARE® Infants' Drops*** are fruit flavored alcohol free and red in color. ***PEDIACARE® Infants' Drops Decongestant Plus Cough*** are cherry flavored, alcohol free and clear, non-staining in color. ***PEDIACARE® Cough-Cold Chewable Tablets*** are fruit flavored and pink in color.

ACTIONS

PEDIACARE Products are available in four different formulas, allowing you to select the ideal product to temporarily relieve the patient's symptoms. ***PEDIACARE® Cough-Cold Liquid*** and ***Chewable Tablets*** contain an antihistamine, chlorpheniramine maleate, a nasal decongestant, pseudoephedrine HCl and a cough suppressant, dextromethorphan hydrobromide, to provide temporary relief of nasal congestion, runny nose, sneezing and coughing due to the common cold, hay fever or other upper respiratory allergies. ***PEDIACARE® NightRest Cough-Cold Liquid*** contains a decongestant, pseudoephedrine hydrochloride, an antihistamine, chlorpheniramine maleate, and a cough suppressant, dextromethorphan hydrobromide, to provide temporary relief of coughs, nasal congestion, runny nose and sneezing due to the common cold hayfever or other upper respiratory allergies. ***PEDIACARE® NightRest*** may be used day or night to relieve cough and cold symptoms. ***PEDIACARE® Infants' Drops Decongestant*** contain a decongestant, pseudoephedrine hydrochloride, to provide temporary relief of nasal congestion due to the common cold, hay fever or other upper respiratory allergies. ***PEDIACARE® Infants' Drops Decongestant Plus Cough*** contain a decongestant, pseudoephedrine hydrochloride, and a cough suppressant, dextromethorphan hydrobromide to provide temporary relief of nasal congestion and coughing due to common cold, hay fever or other upper respiratory allergies.

PROFESSIONAL DOSAGE

A calibrated dosage cup is provided for accurate dosing of the ***PEDIACARE*** Liquid formulas. A calibrated oral dropper is provided for accurate dosing of ***PEDIACARE® Infants' Drops.*** All doses of ***PEDIACARE® Cough-Cold Liquid*** and ***Chewable Tablets***, as well as ***PEDIACARE® Infants' Drops*** may be repeated every 4–6 hours, not to exceed 4 doses in 24 hours. ***PEDIACARE® NightRest Liquid*** may be repeated every 6–8 hrs, not to exceed 4 doses in 24 hours.
[See table below.]

WARNINGS

DO NOT USE IF CARTON IS OPENED, OR IF PRINTED PLASTIC BOTTLE WRAP OR FOIL INNER SEAL IS BROKEN. KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. IN CASE OF ACCIDENTAL OVERDOSAGE, CONTACT A PHYSICIAN OR POISON CONTROL CENTER IMMEDIATELY.
The following information appears on the appropriate package labels:
PEDIACARE® Cough-Cold Chewable Tablets:
PHENYLKETONURICS: CONTAINS PHENYLALANINE 6MG PER TABLET.
PEDIACARE® Cough-Cold Liquid and Chewable Tablets, Night Rest Cough-Cold Liquid: Do not exceed recommended dosage. If nervousness, dizziness or sleeplessness occur, discontinue use and consult a doctor. If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor. A persistent cough may be a sign of a serious condition. If cough persists for more than one week, tends to recur or is accompanied by fever, rash, or persistent headache, consult a doctor. Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor. May cause excitability especially in children. May cause drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers without first consulting the child's doctor. Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, heart disease, high blood pressure, thyroid disease or diabetes, without first consulting the child's doctor.
PEDIACARE® Infants' Drops Decongestant: Do not exceed the recommended dosage. If nervousness, dizziness or sleeplessness occur discontinue use and consult a doctor. If symptoms do not improve within 7 days or are accompanied by fever, consult a physician. Do not give this product to a child who has heart disease, high blood pressure, thyroid disease or diabetes unless directed by a doctor. Take by mouth only. Not for nasal use.
PEDIACARE® Infants' Drops Decongestant Plus Cough: **Do not exceed recommended dosage.** If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor. If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor. A persistent cough may be a sign of a serious condition. If cough persists for more than one week, tends to recur or is accompanied by fever, rash, or persistent headache, consult a doctor. Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor. Do not give this product to a child who has heart disease, high blood pressure, thyroid disease or diabetes unless directed by a doctor. Take by mouth only. Not for nasal use.

DRUG INTERACTION PRECAUTION

Do not give this product to a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your child's prescription drug contains an MAOI, consult a health professional before giving this product.

INACTIVE INGREDIENTS

PEDIACARE® Cough-Cold Liquid: Citric acid, corn syrup, flavors, glycerin, propylene glycol, sodium benzoate, sodium carboxymethylcellulose, sorbitol, purified water and Red #40.
PEDIACARE® NightRest Cough-Cold Liquid: Citric acid, corn syrup, flavors, glycerin, propylene glycol, sodium benzo-

Age Group	0–3 mos	4–11 mos	12–23 mos	2–3 yrs	4–5 yrs	6–8 yrs	9–10 yrs	11 yrs	Dosage
Weight (lbs)	6–11 lb	12–17 lb	18–23 lb	24–35 lb	36–47 lb	48–59 lb	60–71 lb	72–95 lb	
PEDIACARE® Infants' Drops Decongestant*	½ dropper (0.4 ml)	1 dropper (0.8 ml)	1½ droppers (1.2 ml)	2 droppers (1.6 ml)					q4–6h
PEDIACARE® Infants' Drops Decongestant Plus Cough*	½ dropper (0.4 ml)	1 dropper (0.8 ml)	1½ droppers (1.2 ml)	2 droppers (1.6 ml)					q4–6h
PEDIACARE® Cough-Cold Liquid**				1 tsp	1½ tsp	2 tsp	2½ tsp	3 tsp	q4–6h
and Chewable Tablets**				1 tab	1½ tabs	2 tabs	2½ tabs	3 tabs	q4–6h
PEDIACARE® NightRest Liquid**				1 tsp	1½ tsp	2 tsp	2½ tsp	3 tsp	q6–8h

* Administer to children under 2 years only on the advice of a physician.
** Administer to children under 6 years only on the advice of a physician.

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ate, sodium carboxymethylcellulose, sorbitol, purified water and Red #40.
PEDIACARE® Cough-Cold Chewable Tablets: Aspartame, cellulose, citric acid, flavors, magnesium stearate, magnesium trisilicate, mannitol, corn starch and Red #7.
PEDIACARE® Infants' Drops Decongestant: Benzoic acid, citric acid, flavors, glycerin, polyethylene glycol, propylene glycol, purified water, sodium benzoate, sorbitol, sucrose and Red #40.
PEDIACARE® Infants's Drops Decongestant Plus Cough: Citric acid, flavors, glycerin, purified water, sodium benzoate, and sorbitol.

OVERDOSAGE

Acute dextromethorphan overdose usually does not result in serious signs and symptoms unless massive amounts have been ingested. Signs and symptoms of a substantial overdose may include nausea and vomiting, visual disturbances, CNS disturbances, and urinary retention. Symptoms from pseudoephedrine overdose consist most often of mild anxiety, tachycardia and/or mild hypertension. Symptoms usually appear within 4 to 8 hours of ingestion and are transient, usually requiring no treatment. Chlorpheniramine toxicity should be treated as you would an antihistamine/anticholinergic overdose and is likely to be present within a few hours after acute ingestion. Symptoms from pseudoephedrine overdose consist often of mild anxiety, tachycardia and/or mild hypertension. Symptoms usually appear within 4 to 8 hours of ingestion and are transient, usually requiring no treatment.

HOW SUPPLIED

PEDIACARE® Cough-Cold Liquid and NightRest Cough-Cold Liquid (colored red)—bottles of 4 fl. oz. (120 ml) with child-resistant safety cap and calibrated dosage cup. ***PEDIACARE Cough-Cold Chewable Tablets*** (pink, scored)—blister packs of 16. ***PEDIACARE® Infants' Drops Decongestant*** (colored red) and ***PEDIACARE® Infants' Drops Decongestant Plus Cough*** (clear)—bottles of ½ fl. oz (15 ml) with calibrated dropper.

Shown in Product Identification Guide, page 322

Maximum Strength OTC
SINE-AID®
Sinus Medication Gelcaps, Caplets and Tablets

DESCRIPTION

Each ***Maximum Strength SINE-AID® Gelcap, Caplet*** or ***Tablet*** contains acetaminophen 500 mg and pseudoephedrine hydrochloride 30 mg.

ACTIONS

Maximum Strength SINE-AID® Gelcaps, Caplets and ***Tablets*** contain a clinically proven analgesic-antipyretic and a decongestant. Maximum allowable non-prescription levels of acetaminophen and pseudoephedrine provide temporary relief of sinus congestion and pain. Acetaminophen is equal to aspirin in analgesic and antipyretic effectiveness and it is unlikely to produce many of the side effects associated with aspirin and aspirin-containing products. Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center. Pseudoephedrine hydrochloride is a sympathomimetic amine that promotes sinus cavity drainage by reducing nasopharyngeal mucosal congestion.

INDICATIONS

Maximum Strength SINE-AID® Gelcaps, Caplets and ***Tablets*** provide effective symptomatic relief from sinus headache pain and congestion. SINE-AID® is particularly well-suited in patients with aspirin allergy, hemostatic disturbances (including anticoagulant therapy), and bleeding diatheses (e.g. hemophilia) and upper gastrointestinal disease (e.g. ulcer, gastritis, hiatus hernia).

PRECAUTIONS

If a rare sensitivity occurs, the drug should be discontinued. Although pseudoephedrine is virtually without pressor effect in normotensive patients, it should be used with caution in hypertensives.

DIRECTIONS

Adults & children 12 years of age and older: Two gelcaps, caplets or tablets every four to six hours. Do not exceed eight gelcaps, caplets or tablets in any 24 hour period. Not for use in children under 12 years of age.

WARNINGS

Do not use if carton is open or if blister unit is broken.
Do not take for pain for more than 7 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists, or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. **Do not exceed recommended dosage.** If nervousness, dizziness or sleeplessness occur, discontinue use and consult a doctor. Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor.
As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. Keep this and all drugs out of the reach of children. In case of accidental overdose, contact a doctor or poison control center immediately. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms. Do not use with other products containing acetaminophen.

ALCOHOL WARNING

For this and all other pain relievers, including aspirin, ibuprofen, ketoprofen and naproxen sodium, if you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take pain relievers.

DRUG INTERACTION PRECAUTION

Do not use this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

OVERDOSAGE INFORMATION

Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In adults and adolescents, hepatic toxicity has rarely been reported following ingestion of acute overdoses of less than 10 grams. Fatalities are infrequent (less than 3–4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children, an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity.
Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion.
In adults and adolescents, regardless of the quantity of acetaminophen reported to have been ingested, administer acetylcysteine immediately if 24 hours or less have elapsed from the reported time of ingestion. For full prescribing information, refer to the acetylcysteine package insert. Do not await results of assays for plasma acetaminophen level before initiating treatment with acetylcysteine. The following additional procedures are recommended: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. A plasma acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, acetylcysteine therapy should be continued. Liver function studies should be obtained initially and repeated at 24-hour intervals.
Serious toxicity or fatalities are extremely infrequent in children, possibly due to differences in the way they metabolize acetaminophen. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount was ingested, obtain a plasma acetaminophen level. The plasma acetaminophen level should be obtained as soon as possible, but no sooner than 4 hours following the ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, the acetylcysteine therapy should be initiated and continued for a full course of therapy. If plasma acetaminophen assay capability is not available, and the estimated acetaminophen ingestion exceeds 150 mg/kg, acetylcysteine therapy should be initiated and continued for a full course of therapy.
For additional emergency information, call your regional poison center or call the Rocky Mountain Poison Center toll-free, (1-800-525-6115).
Symptoms from pseudoephedrine overdose consist most often of mild anxiety, tachycardia and/or mild hypertension. Symptoms usually appear within 4 to 8 hours of ingestion and are transient, usually requiring no treatment.

ALCOHOL INFORMATION

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports almost invariably involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Professionals should alert their patients who regularly consume large amounts of alcohol not to exceed recommended doses of acetaminophen.

INACTIVE INGREDIENTS

Gelcaps: Benzyl Alcohol, Butylparaben, Castor Oil, Cellulose, Corn Starch, Edetate Calcium Disodium, Gelatin, Hydroxypropyl Methylcellulose, Iron Oxide Black, Magnesium Stearate, Methylparaben, Propylparaben, Sodium Lauryl Sulfate, Sodium Propionate, Sodium Starch Glycolate, Titanium Dioxide, FD&C Red #40.
Caplets: Cellulose, Corn Starch, Hydroxypropyl Methylcellulose, Magnesium Stearate, Polyethylene Glycol, Sodium Starch Glycolate, Titanium Dioxide, Blue #1 and Red #40.
Tablets: Cellulose, Corn Starch, Magnesium Stearate and Sodium Starch Glycolate.

HOW SUPPLIED

Gelcaps (colored red and white imprinted "SINE-AID")—blister package of 20 and tamper resistant bottle of 40.
Caplets (colored white imprinted "Maximum SINE-AID")—blister package of 24 and tamper resistant bottle of 50.
Tablets (colored white embossed "SINE-AID")—blister package of 24 and tamper resistant bottle of 50.

Shown in Product Identification Guide, page 323

Extra Strength OTC
TYLENOL® acetaminophen
Gelcaps, Geltabs, Caplets, Tablets

Extra Strength
TYLENOL® acetaminophen
Adult Liquid Pain Reliever

Regular Strength
TYLENOL® acetaminophen
Caplets and Tablets

TYLENOL® Extended Relief
acetaminophen extended release
Caplets

Product information for all dosage forms of Adult TYLENOL acetaminophen have been combined under this heading.

DESCRIPTION

Each ***Extra Strength TYLENOL® Gelcap, Geltab, Caplet, or Tablet*** contains acetaminophen 500 mg.
Each 15 ml (½ fl oz or one tablespoonful) of ***Extra Strength TYLENOL® acetaminophen Adult Liquid Pain Reliever*** contains 500 mg acetaminophen (alcohol 7%).
Each ***Regular Strength TYLENOL® Caplet or Tablet*** contains acetaminophen 325 mg.
Each ***TYLENOL® Extended Relief Caplet*** contains acetaminophen 650 mg.

ACTIONS

Acetaminophen is a clinically proven analgesic and antipyretic. Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center. Acetaminophen is equal to aspirin in analgesic and antipyretic effectiveness and it is unlikely to produce many of the side effects associated with aspirin and aspirin-containing products.
Tylenol Extended Relief uses a unique, patented bilayer caplet. The first layer dissolves quickly to provide prompt relief while the second layer is time released to provide up to 8 hours of relief.

INDICATIONS

For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for the reduction of fever.

DIRECTIONS

Extra Strength TYLENOL® Gelcaps, Geltabs, Caplets, or Tablets: Adults and Children 12 years of Age and Older: Take two gelcaps, geltabs, caplets, or tablets every 4 to 6 hours. Not to exceed 8 gelcaps, geltabs, caplets, or tablets in any 24-hour period. Not for use in children under 12 years of age.
Extra Strength TYLENOL® Adult Liquid Pain Reliever: Adults and Children 12 years of Age and Older: Fill measuring cup once to 2-tablespoon line (1,000 mg) which is equivalent to two 500 mg Extra Strength TYLENOL® Gelcaps, Geltabs, Caplets or Tablets. Take every 4–6 hours. Not more than 4 doses in any 24-hour period, or as directed by a doctor. Not for use in children under 12 years of age.
Regular Strength TYLENOL® Caplets or Tablets: Adults and Children 12 years of Age and Older: Take two caplets or tablets every 4 to 6 hours. No more than a total of 12 caplets or tablets in any 24-hour period, or as directed by a doctor. Children (6–11): ½ to 1 caplet or tablet every 4 to 6 hours, not to exceed 5 doses in 24 hours. Consult a physician for use by children under 6 years of age.
TYLENOL® Extended Relief Caplets: Adults and Children 12 years of Age and Older: Take two caplets every 8 hours, not to exceed 6 caplets in any 24-hour period. TAKE TWO CAPLETS WITH WATER, SWALLOW EACH CAPLET WHOLE. DO NOT CRUSH, CHEW, OR DISSOLVE THE CAPLET. Not for use in children under 12 years of age.

PRECAUTIONS

If a rare sensitivity reaction occurs, the drug should be discontinued.

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ALCOHOL WARNING

For this and all other pain relievers, including aspirin, ibuprofen, ketoprofen and naproxen sodium. if you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take pain relievers.

DRUG INTERACTION PRECAUTION

TYLENOL® ALLERGY SINUS NightTime and TYLENOL® ALLERGY SINUS: Do not use this product if you are now taking a prescription monamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional condition, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health care professional before taking this product.

OVERDOSAGE INFORMATION

Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In adults and adolescents, hepatic toxicity has rarely been reported following ingestion of acute overdoses of less than 10 grams. Fatalities are infrequent (less than 3–4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children, an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity.

Early symptoms following a potentailly hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion. In adults and adolescents, regardless of the quantity of acetaminophen reported to have been ingested, administer acetylcysteine immediately if 24 hours or less have elapsed from the reported time of ingestion. For full prescribing information, refer to the acetylcysteine package insert. Do not await results of assays for plasma acetaminophen level before initiating treatment with acetylcysteine. The following additional procedures are recommended: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. A plasma acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. If plasma level falls above the lower treatment line on the acetaminophen oiverdose nomogram, acetylcysteine therapy should be continued. Liver function studies should be obtained initially and repeated at 24-hour intervals.

Serious toxicity or fatalities are extremely infrequent in children, possibly due to differences in the way they metabolize acetaminophen. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount was ingested, obtain a plasma acetaminophen level. The plasma acetaminophen level should be obtained as soon as possible, but no sooner than 4 hours following the ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, the acetylcysteine therapy should be initiated and continued for a full course of therapy. If plasma acetaminiophen assay capability is not available, and the estimated acetaminophen ingestion exceeds 150 mg/kg, acetylcysteine therapy should be initiated and continued for a full course of therapy.

For additional emergency information, call your regional poison center or call the Rocky Mountain Poison Center toll-free (1–800–525–6115).

Symptoms for pseudoephedrine overdose consist most often of mild anxiety, tachycardia and/or hypertension. Symptoms usually appear within 4 to 8 hours of ingestion and are transient, usually requiring no treatment.

Diphenhydramine and chlorpheniramine toxicity should be treated as ou would an antihistamine/anticholinergic overdose and is likely to be present within a few hours after acute ingestion.

ALCOHOL INFORMATION

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports almost invariably involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Professionals should alert their patienta who regularly consume large amounts of alcohol not to exceed recommended doses of acetaminophen.

INACTIVE INGREDIENTS

TYLENOL® SEVERE ALLERGY Caplets: Cellulose, Corn Starch, Hydroxpropyl, Cellulose, Hydroxypropyl Methylcellulose, Iron Oxide Black, Magnesium Stearate, Polyethylene Glycol, Sodium Citrate, Sodium Starch Glycolate, Titanium Dioxide, Yellow #6 and Yellow #10.

TYLENOL® ALLERGY SINUS NightTime Caplets: Cellulose, Corn Starch, Hydroxypropyl Methylcellulose, Iron Oxide Black, Magnesium Stearate, Polyethylene Glycol, Polysorbate 80, Sodium Citrate, Sodium Starch Glycolate, Titanium Dioxide, Blue #1, and Yellow #10.

TYLENOL® ALLERGY SINUS: **Caplets:** Carnauba Wax, Cellulose, Cornstarch, Hydroxypropyl Cellulose, Hydroxypropyl Methylcellulose, Iron Oxide Black, Magnesium Stearate, Polyethylene Glycol, Sodium Starch Glycolate, Titanium Dioxide, Blue #1, Yellow #6, and Yellow #10. Gelcaps: Benzyl Alcohol, Butylparaben, Castor Oil Cellulose, Cornstarch, Edetate Calcium Disodium, Gelatin, Hydroxypropyl Methylcellulose, Magnesium Stearate, Methylparaben, propylparaben, Sodium Lauryl Sulfate, Sodium Propionate, Sodium Starch Glycolate, Titanium Dioxide, Blue #1 and #2 and Yellow #10.

HOW SUPPLIED

TYLENOL® SEVERE ALLERGY: **Caplets** (dark yellow, imprinted "TYLENOL Severe Allergy") blister packs of 12 and 24.

TYLENOL® ALLERGY SINUS NightTime: **Caplets** (light blue, imprinted "TYLENOL A/S NightTime") child-resistant blister packs of 24.

TYLENOL® ALLERGY SINUS: **Caplets:** (dark yellow, imprinted "TYLENOL Allergy Sinus") Blister packs of 24 and 48.

Gelcaps and Geltabs: (dark green and dark yellow, imprinted "TYLENOL A/S") Blister packs of 24 and 48.

Shown in Product Identification Guide, page 323

TYLENOL® COLD Medication OTC
No Drowsiness Formula
Caplets and Gelcaps

Multi-Symptom Formula
TYLENOL® COLD Medication
Tablets and Caplets

TYLENOL® COLD Multi-Symptom
Hot Medication Liquid Packets

Product information for all dosage forms of TYLENOL COLD have been combined under this heading.

DESCRIPTION

Each ***TYLENOL® COLD Medication No Drowsiness Formula Caplet and Gelcap*** contains acetaminophen 325 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 15 mg.

Each ***Multi-Symptom Formula TYLENOL® COLD Tablet or Caplet*** contains acetaminophen 325 mg, chlorpheniramine maleate 2 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 15 mg.

Each packet of ***TYLENOL® COLD Multi-Symptom Hot Medication*** contains acetaminophen 650 mg, chlorpheniramine maleate 4 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg.

ACTIONS

TYLENOL® COLD Medication No Drowsiness Formula contains a clinically proven analgesic-antipyretic, decongestant and cough suppressant. Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center. Acetaminophen is equal to aspirin in analgesic and antipyretic effectiveness and it is unlikely to produce many of the side effects associated with aspirin and aspirin-containing products. Pseudoephedrine is a sympathomimetic amine which provides temporary relief of nasal congestion. Dextromethorphan is a cough suppressant which provides temporary relief of coughs due to minor throat irritations that may occur with the common cold.

Multi-Symptom Formula TYLENOL® COLD Medication and ***TYLENOL® COLD Multi-Symptom Hot Medication*** contain, in addition to the above ingredients, an antihistamine. Chlorpheniramine is an antihistamine which helps provide temporary relief of runny nose, sneezing and watery and itchy eyes.

INDICATIONS

TYLENOL® COLD Medication No Drowsiness Formula provides effective temporary relief of nasal congestion, coughing, and body aches, pains, headache, sore throat and fever due to a cold or "flu."

Multi-Symptom Formula TYLENOL® COLD Medication and ***TYLENOL® COLD Multi-Symptom Hot Medication*** provide effective temporary relief of runny nose, sneezing, watery and itchy eyes, nasal congestion, coughing and body aches, pains, headache, sore throat and fever due to a cold or "flu."

DIRECTIONS

TYLENOL® COLD No Drowsiness Formula and Multi-Symptom Formula TYLENOL® COLD Medication: Adults (12 years and older): Two every 6 hours, not to exceed 8 in 24 hours. Children (6–11 years): One every 6 hours, not to exceed 4 in 24 hours. Not for use in children under 6 years of age.

TYLENOL® COLD Multi-Symptom Hot Medication: Adults (12 years and older): dissolve one packet in 6 oz. cup of hot water. Sip while hot. Sweeten to taste, if desired. May repeat every 6 hours, not to exceed 4 doses in 24 hours. Not for use in children under 12 years of age.

PRECAUTIONS

TYLENOL® COLD Medication No Drowsiness Formula, Multi-Symptom Formula TYLENOL® COLD Medication and TYLENOL® COLD Multi-Symptom Hot Medication: If a rare sensitivity reaction occurs, the drug should be stopped. Although pseudoephedrine is virtually without pressor effect in normotensive patients, it should be used with caution in hypertensives.

TYLENOL® COLD Medication No Drowsiness Formula: Do not take this product for more than 7 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists, or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea or vomiting, consult a doctor promptly. A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by fever, rash or persistent headache, consult a doctor. Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, emphysema or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor. Do not exceed recommended dosage because at higher doses, nervousness, dizziness or sleeplessness may occur. Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor. Do not use with other products containing acetaminophen.

DO NOT USE IF CARTON IS OPENED OR IF A BLISTER UNIT IS BROKEN. **KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. AS WITH ANY DRUG, IF YOU ARE PREGNANT OR NURSING A BABY, SEEK THE ADVICE OF A HEALTH PROFESSIONAL BEFORE USING THIS PRODUCT. IN CASE OF ACCIDENTAL OVERDOSE, CONTACT A DOCTOR OR POISON CONTROL CENTER IMMEDIATELY. PROMPT MEDICAL ATTENTION IS CRITICAL FOR ADULTS AS WELL AS FOR CHILDREN EVEN IF YOU DO NOT NOTICE ANY SIGNS OR SYMPTOMS.**

Multi-Symptom Formula TYLENOL® COLD Medication: Do not take this product for more than 7 days or for fever for more than 3 days unless directed by a doctor. If symptoms do not improve or are accompanied by fever, consult a doctor. If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea or vomiting, consult a doctor promptly. A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by fever, rash or persistent headache, consult a doctor. Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, emphysema or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor. Do not exceed recommended dosage because at higher doses, nervousness, dizziness or sleeplessness may occur. May cause excitability in children. Do not take this product unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland. Do not take this product if you have heart disease, high blood pressure, thyroid disease or diabetes unless directed by a doctor. May cause drowsiness; alcohol, sedatives and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery. Do not use with other products containing acetaminophen.

DO NOT USE IF CARTON IS OPENED OR IF A BLISTER UNIT IS BROKEN. **KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. AS WITH ANY DRUG, IF YOU ARE PREGNANT OR NURSING A BABY, SEEK THE ADVICE OF A HEALTH PROFESSIONAL BEFORE USING THIS PRODUCT. IN CASE OF ACCIDENTAL OVERDOSE, CONTACT A DOCTOR OR POISON CONTROL CENTER IMMEDIATELY. PROMPT MEDICAL ATTENTION IS CRITICAL FOR ADULTS AS WELL AS FOR CHILDREN EVEN IF YOU DO NOT NOTICE ANY SIGNS OR SYMPTOMS.**

WARNING

TYLENOL® COLD Multi-Symptom Hot Medication: Do not take this product for more than 7 days or for fever for more than 3 days unless directed by a doctor. If symptoms do not improve or are accompanied by fever, consult a doctor. If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea or vomiting, consult a doctor promptly. A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by fever, rash or persistent headache, consult a doctor. Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, emphysema or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor. Do not exceed recommended dosage because at higher doses, nervousness,

dizziness, sleeplessness may occur. May cause excitability especially in children. Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland. Do not take this product if you have heart disease, high blood pressure, thyroid disease or diabetes unless directed by a doctor. May cause drowsiness; alcohol, sedatives and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery. Do not use with other products containing acetaminophen.

DO NOT USE IF PRINTED CARTON OVERWRAP IS BROKEN OR MISSING OR IF FOIL PACKET IS TORN OR BROKEN. **KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. AS WITH ANY DRUG, IF YOU ARE PREGNANT OR NURSING A BABY, SEEK THE ADVICE OF A HEALTH PROFESSIONAL BEFORE USING THIS PRODUCT. IN CASE OF ACCIDENTAL OVERDOSE, CONTACT A DOCTOR OR POISON CONTROL CENTER IMMEDIATELY. PROMPT MEDICAL ATTENTION IS CRITICAL FOR ADULTS AS WELL AS FOR CHILDREN EVEN IF YOU DO NOT NOTICE ANY SIGNS OR SYMPTOMS. PHENYLKETONURICS: CONTAINS PHENYLALANINE 11 MG PER PACKET.**

ALCOHOL WARNING

For this and all other pain relievers, including aspirin, ibuprofen, ketoprofen and naproxen sodium, if you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take pain relievers.

DRUG INTERACTION PRECAUTION

TYLENOL® COLD Medication No Drowsiness Formula, Multi-Symptom Formula TYLENOL® COLD Medication and TYLENOL® COLD Multi-Symptom Hot Medication: Do not take this product if you are presently taking a prescription drug for high blood pressure or you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

OVERDOSAGE INFORMATION

TYLENOL® COLD Medication No Drowsiness Formula, Multi-Symptom Formula TYLENOL® COLD Medication and TYLENOL® COLD Multi-Symptom Hot Medication: Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In adults and adolescents, hepatic toxicity has rarely been reported following ingestion of acute overdoses of less than 10 grams. Fatalities are infrequent (less than 3–4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children, an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion. In adults and adolescents, regardless of the quantity of acetaminophen reported to have been ingested, administer acetylcysteine immediately if 24 hours or less have elapsed from the reported time of ingestion. For full prescribing information, refer to the acetylcysteine package insert. Do not await results of assays for plasma acetaminophen level before initiating treatment with acetylcysteine. The following additional procedures are recommended. The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. A plasma acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, acetylcysteine therapy should be continued. Liver function studies should be obtained initially and repeated at 24-hour intervals.

Serious toxicity or fatalities are extremely infrequent in children, possibly due to differences in the way they metabolize acetaminophen. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount was ingested, obtain a plasma acetaminophen level. The plasma acetaminophen level should be obtained as soon as possible, but no sooner than 4 hours following the ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, the acetylcysteine therapy should be initiated and continued for a full course of therapy. If plasma acetaminophen assay capability is not available, and the estimated acetaminophen ingestion exceeds 150 mg/kg, acetylcysteine therapy should be initiated and continued for a full course of therapy.

For additional emergency information, call your regional poison center or call the Rocky Mountain Poison Center toll-free, (1-800-525-6115).

Symptoms from pseudoephedrine overdose consist most often of mild anxiety, tachycardia and/or mild hypertension. Symptoms usually appear within 4 to 8 hours of ingestion and are transient, usually requiring no treatment.

Acute dextromethorphan overdose usually does not result in serious signs and symptoms unless massive amounts have been ingested. Signs and symptoms of a substantial overdose may include nausea and vomiting, visual disturbances, CNS disturbances, and urinary retention.

Chlorpheniramine toxicity should be treated as you would an antihistamine/anticholinergic overdose and is likely to be present within a few hours after acute ingestion.

ALCOHOL INFORMATION

TYLENOL® COLD Medication No Drowsiness Formula, Multi-symptom Formula TYLENOL® COLD Medication and TYLENOL® COLD Multi-Symptom Hot Medication: Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports almost invariably involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Professionals should alert their patients who regularly consume large amounts of alcohol not to exceed recommended doses of acetaminophen.

INACTIVE INGREDIENTS

TYLENOL® COLD No Drowsiness Formula: Caplets: cellulose, corn starch, glyceryl triacetate, hydroxypropyl methylcellulose, iron oxide black, magnesium stearate, sodium starch glycolate, titanium dioxide, Blue #1 and Yellow #10. Gelcap: benzyl alcohol, butylparaben, castor oil, cellulose, corn starch, edetate calcium disodium, gelatin, hydroxypropyl methylcellulose, magnesium stearate, methylparaben, propylparaben, sodium propionate, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide, Red #40 and Yellow #10.

Multi-Symptom Formula TYLENOL® COLD Medication: Tablets: cellulose, cornstarch, magnesium stearate, Sodium Starch Glycolate Yellow #6 and Yellow #10. **Caplets:** cellulose, cornstarch, glyceryl triacetate, hydroxypropyl methylcellulose, iron oxide black, magnesium stearate, sodium starch glycolate, titanium dioxide, Blue #1 and Yellow #6 and #10.

TYLENOL® COLD Multi-Symptom Hot Medication: Aspartame, citric acid, corn starch, sodium citrate, sucrose, Red #40 and Yellow #10.

HOW SUPPLIED

TYLENOL® COLD No Drowsiness Formula: Caplets (colored white, imprinted "TYLENOL COLD") blister packs of 24. Gelcaps (colored red and tan, imprinted "TYLENOL COLD") blister packs of 24.

Multi-Symptom Formula TYLENOL® COLD Medication: Tablets (colored yellow, imprinted "TYLENOL Cold") blister packs of 24. **Caplets** (light yellow, imprinted "TYLENOL Cold") blister packs of 24.

TYLENOL® COLD Multi-Symptom Hot Medication: Packets of powder (yellow colored) in cartons of 6 tamper-resistant foil packets.

Shown in Product Identification Guide, page 323

MULTI-SYMPTOM TYLENOL® COLD SEVERE CONGESTION — OTC

DESCRIPTION

EACH CAPLET contains acetaminophen 325 mg, pseudoephedrine HCl 30 mg, guaifenesin 200 mg and dextromethorphan HBr 15 mg.

ACTIONS

Multi-Symptom ***TYLENOL® COLD SEVERE CONGESTION Caplets*** contains a clinically proven analgesic-antipyretic, decongestant, expectorant and cough suppressant. Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center. Acetaminophen is equal to aspirin in analgesic and antipyretic effectiveness and is unlikely to produce many of the side effects associated with aspirin and aspirin-containing products. Pseudoephedrine is a sympathomimetic amine which provides temporary relief of nasal congestion. Guaifenesin is an expectorant which helps loosen phlegm (mucus) and thin bronchial secretions to make coughs more productive. Dextromethorphan is a cough suppressant which provides temporary relief of coughs due to minor throat irritations that may occur with the common cold.

INDICATIONS

Multi-Symptom ***TYLENOL® COLD SEVERE CONGESTION Caplets*** provide temporary relief without drowsiness of nasal congestion, chest congestion, coughing, sore throat, headaches, body aches and fever.

DOSAGE

Adults and Children 12 years of Age and older: Take two caplets every 6–8 hours, not to exceed 8 caplets in any 24 hour period.

Children 6 to 11 years of age: One caplet every 6–8 hours not to exceed 4 caplets in any 24 hour period. Not for use in children under 6 years of age.

PRECAUTIONS

If a rare sensitivity reaction occurs, the drug should be discontinued. Although pseudoephedrine is virtually without pressor effect in normotensive patients, it should be used with caution in hypertensives.

WARNINGS

DO NOT USE IF CARTON IS OPENED OR IF A BLISTER UNIT IS BROKEN. Do not take for pain for more than 7 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists, or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea or vomiting, consult a doctor promptly. A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by fever, rash or persistent headache, consult a doctor. Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, emphysema or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor. **Do not exceed recommended dosage.** If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor. Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. Keep this and all drugs out of the reach of children., In case of accidental overdose, contact a doctor or poison control center immediately. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs of symptoms. Do not use with other products containing acetaminophen.

ALCOHOL WARNING

For this and all other pain relievers, including aspirin, ibuprofen, ketoprofen and naproxen sodium, if you generally consume 3 or more alcohol-containing drinks per day you should consult your physician for advice on when and how you should take pain relievers.

OVERDOSAGE INFORMATION

Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In adults and adolescents, hepatic toxicity has rarely been reported following ingestion of acute overdoses of less than 10 grams. Fatalities are infrequent (less than 3–4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children, an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion. In adults and adolescents, regardless of the quantity of acetaminophen reported to have been ingested, administer acetylcysteine immediately if 24 hours or less have elapsed from the reported time of ingestion. For full prescribing information, refer to the acetylcysteine package insert. Do not await results of assays for plasma acetaminophen level before initiating treatment with acetylcysteine. The following additional procedures are recommended. The stomach should be emptied promptly by lavage or by inducing of emesis with syrup of ipecac. A plasma acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, acetylcysteine therapy should be continued. Liver function studies should be obtained initially and repeated at 24-hour intervals.

Serious toxicity or fatalities are extremely infrequent in children, possibly due to differences in the way they metabolize acetaminophen. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount was ingested, obtain a plasma acetaminophen level. The plasma acetaminophen level should be obtained as soon as possible, but no sooner than 4 hours following the ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, the acetylcysteine therapy should be initiated and continued for a full course of therapy. If plasma acetaminophen assay capability is not available, and the

Continued on next page

McNeil Consumer—Cont.

estimated acetaminophen ingestion exceeds 150 mg/kg, acetlcysteine therapy should be initiated and continued for a full course of therapy.
For additional emergency information, call your regional poison center or call the Rocky Mountain Poison Center toll-free, (1-800-525-6115).
Symptoms from pseudoephedrine overdose consist most often of mild anxiety, tachycardia and/or mild hypertension. Symptoms usually appear within 4 to 8 hours of ingestion and are transient, usually requiring no treatment.
Acute dextromethorphan overdose usually does not result in serious signs and symptoms unless massive amounts have been ingested. Signs and symptoms of a substantial overdose may include nausea and vomiting, visual disturbance, CNS disturbances, and urinary retention.
Chlorpheniramine toxicity should be treated as you would an antihistamine/anticholinergic overdose and is likely to be present within a few hours after acute ingestion. Guaifenesin should be treated as a non-toxic ingestion.

ALCOHOL INFORMATION

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports almost invariably involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Professionals should alert their patients who regularly consume large amounts of alcohol not to exceed recommended doses of acetaminophen.

DRUG INTERACTION PRECAUTION

Do not use this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stoppping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

INACTIVE INGREDIENTS

Carnauba Wax, Cellulose, Colloidal Silicon Dioxide, Corn Starch, Hydroxypropyl Methylcellulose, Iron Oxide, Povidone, Pregelatinized Starch, Propylene Glycol, Sodium Starch Glycolate, Stearic Acid, Titanium Dioxide, Triacetin, Blue #1, Yellow #6 and Yellow #10.

HOW SUPPLIED

Caplets (colored buttery-tan, with green imprinted "TYLENOL COLD SC") in blister packs of 12 and 24.
 8702830
Shown in Product Identification Guide, page 323

Multi-Symptom
TYLENOL® COUGH Medication **OTC**

Multi-Symptom
TYLENOL® COUGH Medication
with Decongestant

Product information for all dosage forms of TYLENOL COUGH have been combined under this heading.

DESCRIPTION

Each 15 ml (3 tsp.) adult dose of ***Multi-Symptom TYLENOL® COUGH Medication*** contains dextromethorphan HBr 30 mg, and acetaminophen 650 mg.
Each 15 ml (3 tsp.) adult dose of ***Multi-Symptom TYLENOL® COUGH Medication with Decongestant*** contains dextromethorphan HBr 30 mg, acetaminophen 650 mg, and pseudoephedrine HCl 60 mg.

ACTIONS

Multi-Symptom TYLENOL® COUGH Medication contains a clinically proven cough suppressant, and an analgesic-antipyretic. Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center. Dextromethorphan is a cough suppressant which provides temporary relief of coughs due to minor throat irritations that may occur with the common cold.
Multi-Symptom TYLENOL® COUGH Medication with Decongestant contains, in addition to the above ingredients, a sympathomimetic amine, pseudoephedrine HCl, which provides temporary relief of nasal congestion.

INDICATIONS

Multi-Symptom TYLENOL® COUGH Medication provides effective, temporary relief of coughing, and the aches, pains and sore throat that may accompany a cough due to a cold.
Multi-Symptom TYLENOL® COUGH Medication with Decongestant provides effective, temporary relief of coughing, nasal congestion and the aches, pains and sore throat that may accompany a cough due to a cold.

DIRECTIONS

Multi-Symptom TYLENOL® COUGH Medication and Multi-Symptom TYLENOL® COUGH Medication with Decongestant: Adults (12 years and older): 1 tablespoon or 3 teaspoons every 6–8 hours, not to exceed 4 doses in 24 hours. Children: (ages 6–11) $1^1/_2$ teaspoons every 6–8 hours, not to exceed 4 doses in 24 hours. Not for use in children under 6 years of age.

PRECAUTIONS

Multi-Symptom TYLENOL® COUGH Medication: If a rare sensitivity reaction occurs, the drug should be discontinued.
Multi-Symptom TYLENOL® COUGH Medication with Decongestant: If a rare sensitivity reaction occurs, the drug should be discontinued. Although pseudoephedrine is virtually without pressor effect in normotensive patients, it should be used with caution in hypertensives.

WARNING

Multi-Symptom TYLENOL® COUGH Medication: Do not take this product for more than 10 days or for fever for more than 3 days unless directed by a physician. Severe or recurrent pain or high or continued fever may be indicative of serious illness. Under these conditions, consult a doctor. A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by fever, rash or persistent headache, consult a doctor. Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor. If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea or vomiting, consult a doctor promptly. Do not use with other products containing acetaminophen.
DO NOT USE IF PRINTED PLASTIC BOTTLE WRAP OR PRINTED FOIL INNER SEAL IS BROKEN. **As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. Keep this and all medication out of the reach of children. In case of accidental overdosage, contact a doctor or poison control center immediately. Prompt medical attention is critical for adults as well as children even if you do not notice any signs or symptoms.**
Multi-Symptom TYLENOL® COUGH Medication with Decongestant: Do not take this product for more than 7 days or for fever for more than 3 days unless directed by a doctor. If symptoms do not improve or are accompanied by fever, consult a doctor. A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by fever, rash or persistent headache, consult a doctor. Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor. Do not exceed the recommended dosage because at higher doses nervousness, dizziness or sleeplessness may occur. Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor. If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea or vomiting, consult a doctor promptly. Do not use with other products containing acetaminophen.
DO NOT USE IF PRINTED PLASTIC BOTTLE WRAP OR PRINTED FOIL INNER SEAL IS BROKEN. **As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. Keep this and all medication out of the reach of children. In case of accidental overdosage, contact a doctor or poison control center immediately. Prompt medical attention is critical for adults as well as children even if you do not notice any signs or symptoms.**

ALCOHOL WARNING

Multi-Symptom TYLENOL® COUGH Medication and Multi-Symptom TYLENOL® COUGH Medication with Decongestant: For this and all other pain relievers, including aspirin, ibuprofen, ketoprofen and naproxen sodium; if you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take pain relievers.

DRUG INTERACTION PRECAUTION

Multi-Symptom TYLENOL® COUGH Medication: Do not use this product if you are presently taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's Disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.
Multi-Symptom TYLENOL® COUGH Medication with Decongestant: Do not use this product if you are presently taking a prescription drug for high blood pressure or you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression or psychiatric or emotional conditions, or Parkinson's Disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

OVERDOSAGE INFORMATION

Multi-Symptom TYLENOL® COUGH Medication and Multi-Symptom TYLENOL® COUGH Medication with Decongestant: Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In adults and adolescents, hepatic toxicity has rarely been reported following ingestion of acute overdoses of less than 10 grams. Fatalities are infrequent (less than 3–4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children, an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity.
Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion. In adults and adolescents, regardless of the quantity of acetaminophen reported to have been ingested, administer acetylcysteine immediately if 24 hours or less have elapsed from the reported time of ingestion. For full prescribing information, refer to the acetylcysteine package insert. Do not await results of assays for plasma acetaminophen level before initiating treatment with acetylcysteine. The following additional procedures are recommended. The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. A plasma acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, acetylcysteine therapy should be continued. Liver function studies should be obtained initially and repeated at 24-hour intervals.
Serious toxicity or fatalities are extremely infrequent in children, possibly due to differences in the way they metabolize acetaminophen. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount was ingested, obtain a plasma acetaminophen level. The plasma acetaminophen level should be obtained as soon as possible, but no sooner than 4 hours following the ingestion. If the plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, the acetylcysteine therapy should be initiated and continued for a full course of therapy. If plasma acetaminophen assay capability is not available, and the estimated acetaminophen ingestion exceeds 150 mg/kg, acetycysteine therapy should be initiated and continued for a full course of therapy.
For additional emergency information, call your regional poison center or call the Rocky Mountain Poison Center toll-free (1-800-525-6115).
Acute dextromethorphan overdose usually does not result in serious signs and symptoms unless massive amounts have been ingested. Signs and symptoms of a substantial overdose may include nausea and vomiting, visual disturbances, CNS disturbances, and urinary retention.
Symptoms from pseudoephedrine overdose consist most often of mild anxiety, tachycardia and/or mild hypertension. Symptoms usually appear within 4 to 8 hours of ingestion and are transient, usually requiring no treatment.

ALCOHOL INFORMATION

Multi-Symptom TYLENOL® COUGH Medication and Multi-Symptom TYLENOL® COUGH Medication with Decongestant: Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports almost invariably involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Professionals should alert their patients who regularly consume large amounts of alcohol not to exceed recommended doses of acetaminophen.

INACTIVE INGREDIENTS

Multi-Symptom TYLENOL® COUGH Medication: Alcohol (5%), citric acid, flavors, high fructose corn syrup, polyethylene glycol, propylene glycol, purified water, sodium benzoate, sodium carboxymethylcellulose, sodium saccharin, sorbitol, Red #40.
Multi-Symptom TYLENOL® COUGH Medication with Decongestant: Alcohol (5%), citric acid, flavors, high fructose corn syrup. polyethylene glycol, propylene glycol, purified water, sodium benzoate, sodium carboxymethylcellulose, sodium saccharin, sorbitol, Blue #1, and Red #40.

HOW SUPPLIED

Multi-Symptom TYLENOL® COUGH Medication is available in a 4 oz. bottle with child resistant safety cap and tamper resistant packaging.
Multi-Symptom TYLENOL® COUGH Medication with Decongestant is available in a 4 oz. bottle with child resistant safety cap, and tamper resistant packaging.
Shown in Product Identification Guide, page 323

Maximum Strength **OTC**
TYLENOL® FLU Medication
No Drowsiness Formula Gelcaps

Maximum Strength
TYLENOL® FLU NightTime
Medication Gelcaps

Maximum Strength
TYLENOL® FLU NightTime
Hot Medication Packets

Product information for all dosage forms of TYLENOL FLU have been combined under this heading.

DESCRIPTION

Each ***Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula Gelcap*** contains acetaminophen 500 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 15 mg.

Each ***Maximum Strength TYLENOL® FLU NightTime Medication Gelcap*** contains acetaminophen 500 mg, pseudoephedrine hydrochloride 30 mg, and diphenhydramine hydrochloride 25 mg.

Each packet of ***Maximum Strength TYLENOL FLU NightTime Hot Medication*** contains acetaminophen 1000 mg, pseudoephedrine hydrochloride 60 mg and diphenhydramine hydrochloride 50 mg.

ACTIONS

Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula contains a clinically proven analgesic-antipyretic, decongestant and cough suppressant. Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center. Acetaminophen is equal to aspirin in analgesic and antipyretic effectiveness and it is unlikely to produce many of the side effects associated with aspirin and aspirin-containing products. Pseudoephedrine hydrochloride is a sympathomimetic amine which provides temporary relief of nasal congestion. Dextromethorphan is a cough suppressant which provides temporary relief of coughs due to minor throat irritations that may occur with the common cold.

Maximum Strength TYLENOL® FLU NightTime Medication and ***Maximum Strength TYLENOL® FLU NightTime Hot Medication*** contains the same clinically proven analgesic-antipyretic and decongestant as Maximum Strength TYLENOL FLU Medication No Drowsiness Formula along with an antihistamine. Diphenhydramine is an antihistamine which helps provide temporary relief of runny nose and sneezing.

INDICATIONS

Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula provides effective temporary relief of body aches, headaches, fever, sore throat, coughing and nasal congestion due to a cold or "flu."

Maximum Strength TYLENOL® FLU NightTime Medication and ***Maximum Strength TYLENOL® FLU NightTime Hot Medication*** provides effective temporary relief of body aches, headaches, fever, sore throat, nasal congestion, and runny nose/sneezing due to a cold or "flu" so you can rest.

DIRECTIONS

Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula: Adults (12 years and older): Two gelcaps every 6 hours, not to exceed 8 gelcaps in 24 hours. Not for use in children under 12 years of age.

Maximum Strength TYLENOL® FLU NightTime Medication: Adults (12 years and older): Two gelcaps at bedtime. May repeat every 6 hours, not to exceed 8 gelcaps in 24 hours. Not for use in children under 12 years of age.

Maximum Strength TYLENOL® FLU NightTime Hot Medication: Adults (12 years and older): Dissolve one packet in 6 oz. cup of hot water. Sip while hot. Sweeten to taste, if desired. May repeat every 6 hours, not to exceed 4 doses in 24 hours. Not for use in children under 12 years of age.

PRECAUTIONS

Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula, Maximum Strength TYLENOL® FLU NightTime Medication, and Maximum Strength TYLENOL® FLU NightTime Hot Medication: If a rare sensitivity reaction occurs, the drug should be stopped. Although pseudoephedrine is virtually without pressor effect in normotensive patients, it should be used with caution in hypertensives.

WARNINGS

Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula: Do not take this product for more than 7 days or for fever for more than 3 days unless directed by a doctor. If symptoms do not improve or are accompanied by fever, consult a doctor. A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by fever, rash or persistent headache, consult a doctor. Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, emphysema or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor. If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea or vomiting, consult a doctor promptly. Do not exceed recommended dosage because at higher doses, nervousness, dizziness or sleeplessness may occur. Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor. Do not use with other products containing acetaminophen.

DO NOT USE IF CARTON IS OPENED OR IF A BLISTER UNIT IS BROKEN. KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. AS WITH ANY DRUG, IF YOU ARE PREGNANT OR NURSING A BABY, SEEK THE ADVICE OF A HEALTH PROFESSIONAL BEFORE USING THIS PRODUCT. IN CASE OF ACCIDENTAL OVERDOSE, CONTACT A DOCTOR OR POISON CONTROL CENTER IMMEDIATELY. PROMPT MEDICAL ATTENTION IS CRITICAL FOR ADULTS AS WELL AS CHILDREN EVEN IF YOU DO NOT NOTICE ANY SIGNS OR SYMPTOMS.

Maximum Strength TYLENOL® FLU NightTime Medication Gelcaps: Do not exceed the recommended dosage, because at higher doses, nervousness, dizziness or sleeplessness may occur. Do not take this product for more than 7 days or for fever for more than 3 days unless directed by a doctor. If symptoms do not improve or are accompanied by fever, consult a doctor. If sore throat is severe, persists for more than 2 days, is accompanied by fever, headache, rash nausea or vomiting, consult a doctor promptly. May cause excitability, especially in children. Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland. Do not take this product if you have heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor. May cause marked drowsiness: alcohol, sedatives and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery. Do not use with other products containing acetaminophen.

DO NOT USE IF CARTON IS OPENED OR IF A BLISTER UNIT IS BROKEN. KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. AS WITH ANY DRUG, IF YOU ARE PREGNANT OR NURSING A BABY, SEEK THE ADVICE OF A HEALTH PROFESSIONAL BEFORE USING THIS PRODUCT. IN CASE OF ACCIDENTAL OVERDOSE, CONTACT A DOCTOR OR POISON CONTROL CENTER IMMEDIATELY. PROMPT MEDICAL ATTENTION IS CRITICAL FOR ADULTS AS WELL AS CHILDREN EVEN IF YOU DO NOT NOTICE ANY SIGNS OR SYMPTOMS.

Maximum Strength TYLENOL® FLU NightTime Hot Medication: Do not exceed the recommended dosage, because at higher doses, nervousness, dizziness or sleeplessness may occur. Do not take this product for more than 7 days or for fever for more than 3 days unless directed by a doctor. If symptoms do not improve or are accompanied by fever, consult a doctor. If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea or vomiting, consult a doctor promptly. May cause excitability especially in children. Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland. Do not take this product if you have heart disease, high blood pressure, thyroid disease or diabetes unless directed by a doctor. May cause marked drowsiness: alcohol, sedatives and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery. Do not use with other products containing acetaminophen.

DO NOT USE IF PRINTED CARTON OVERWRAP IS BROKEN OR MISSING OR IF CARTON IS OPENED OR FOIL PACKET IS TORN OR BROKEN. KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. AS WITH ANY DRUG, IF YOU ARE PREGNANT OR NURSING A BABY, SEEK THE ADVICE OF A HEALTH PROFESSIONAL BEFORE USING THIS PRODUCT. IN CASE OF ACCIDENTAL OVERDOSE, CONTACT A DOCTOR OR POISON CONTROL CENTER IMMEDIATELY. PROMPT MEDICAL ATTENTION IS CRITICAL FOR ADULTS AS WELL AS CHILDREN EVEN IF YOU DO NOT NOTICE ANY SIGNS OR SYMPTOMS.

PHENYLKETONURICS: CONTAINS PHENYLALANINE 67 MG PER PACKET.

ALCOHOL WARNING

Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula, Maximum Strength TYLENOL® FLU NightTime Medication, and Maximum Strength TYLENOL® FLU NightTime Hot Medication: For this and all other pain relievers, including aspirin, ibuprofen, ketoprofen and naproxen sodium, if you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take pain relievers.

DRUG INTERACTION PRECAUTION

Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula, Maximum Strength TYLENOL® FLU NightTime Medication, and Maximum Strength TYLENOL® FLU NightTime Hot Medication: Do not take this product if you are presently taking a prescription drug for high blood pressure or you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

OVERDOSAGE INFORMATION

Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula, Maximum Strength TYLENOL® FLU NightTime Medication, and Maximum Strength TYLENOL® FLU NightTime Hot Medication: Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In adults and adolescents, hepatic toxicity has rarely been reported following ingestion of acute overdoses of less than 10 grams. Fatalities are infrequent (less than 3–4% of untreated cases) and have rarely been reported with overdosage of less than 15 grams. In children, an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion. In adults and adolescents, regardless of the quantity of acetaminophen reported to have been ingested, administer acetylcysteine immediately if 24 hours or less have elapsed from the reported time of ingestion. For full prescribing information, refer to the acetylcysteine package insert. Do not await results of assays for plasma acetaminophen level before initiating treatment with acetyleysteine. The following additional procedures are recommended: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. A plasma acetaminophen assay should be obtained as early as possible, but not sooner than four hours following ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, acetylcysteine therapy should be continued. Liver function studies should be obtained initially and repeated at 24-hour intervals.

Serious toxicity or fatalities are extremely infrequent in children, possibly due to differences in the way they metabolize acetaminophen. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount was ingested, obtain an plasma acetaminophen level. The plasma acetaminophen level should be obtained as soon as possible, but no sooner than 4 hours following the ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, the acetylcysteine therapy should be initiated and continued for a full course of therapy. If plasma acetaminophen assay capability is not available, and the estimated acetaminophen ingestion exceeds 150 mg/kg, acetylcysteine therapy should be initiated and continued for a full course of therapy.

For additional emergency information, call your regional poison center or call the Rocky Mountain Poison Center toll-free, (1-800-525-6115).

Symptoms from pseudoephedrine overdose consist most often of mild anxiety, tachycardia and/or mild hypertension. Symptoms usually appear within 4 to 8 hours of ingestion and are transient, usually requiring no treatment.

Acute dextromethorphan overdose usually does not result in serious signs and symptoms unless massive amounts have been ingested. Signs and symptoms of a substantial overdose may include nausea and vomiting, visual disturbances, CNS disturbances, and urinary retention.

Diphenhydramine toxicity should be treated as you would an antihistamine/anticholinergic overdose and is likely to be present within a few hours after acute ingestion.

ALCOHOL INFORMATION

Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula, Maximum Strength TYLENOL® FLU NightTime Medication, and Maximum Strength TYLENOL® FLU NightTime Hot Medication: Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports almost invariably involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Professionals should alert their patients who regularly consume large amounts of alcohol not to exceed recommended doses of acetaminophen.

Continued on next page

McNeil Consumer—Cont.

INACTIVE INGREDIENTS

Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula: Benzyl alcohol, butylparaben, castor oil, cellulose, corn starch edetate calcium disodium, gelatin, hydroxypropyl methylcellulose, iron oxide black, magnesium stearate, methylparaben, propylparaben, sodium lauryl sulfate, sodium propionate, sodium starch glycolate, titanium dioxide, Red #40 and Blue #1.

Maximum Strength TYLENOL® FLU NightTime Medication: Benzyl alcohol, butylparaben, castor oil, cellulose, corn starch, edetate calcium disodium, gelatin, hydroxypropyl methylcellulose, iron oxide black, magnesium stearate, methylparaben, propylparaben, sodium citrate, sodium laurel sulfate, sodium propionate, sodium starch glycolate, titanium dioxide, Red #28 and Blue #1.

Maximum Strength TYLENOL® FLU Hot Medication Packets: Ascorbic acid (vitamin C), aspartame, citric acid, flavors, sodium citrate, sucrose, Yellow #10, Blue #1, Red #40, and Yellow #6. May also contain: silicon dioxide.

HOW SUPPLIED

Maximum Strength TYLENOL® FLU Medication No Drowsiness Formula: **Gelcaps** (colored burgundy and white, imprinted "TYLENOL FLU") in blister packs of 10 and 20.

Maximum Strength TYLENOL® FLU NightTime Medication: **Gelcaps** (colored blue and white, imprinted "TYLENOL FLU NT") in blister packs of 10 and 20.

Maximum Strength TYLENOL® FLU Hot Medication Packets: **Packets of powder** (yellow colored) in cartons of 6 tamper-resistant foil packets.

Shown in Product Identification Guide, page 323

Extra Strength **OTC**

TYLENOL® PM

Pain Reliever/Sleep Aid Caplets, Geltabs and Gelcaps

DESCRIPTION

Each ***Extra Strength TYLENOL® PM Caplet, Geltab*** or ***Gelcap*** contains acetaminophen 500 mg and diphenhydramine HCl 25 mg.

ACTIONS

Extra Strength TYLENOL® PM Caplets, Geltabs and ***Gelcaps*** contain a clinically proven analgesic-antipyretic and an antihistamine. Maximum allowable non-prescription levels of acetaminophen and diphenhydramine provide temporary relief of occasional headaches and minor aches and pains accompanying sleeplessness. Acetaminophen is equal to aspirin in analgesic and antipyretic effectiveness and it is unlikely to produce many of the side effects associated with aspirin containing products. Acetaminophen produces analgesia by elevation of the pain threshold. Diphenhydramine HCl is an antihistamine with sedative properties.

INDICATIONS

Extra Strength TYLENOL® PM Caplets, Geltabs and ***Gelcaps*** provide temporary relief of occasional headaches and minor aches and pains with accompanying sleeplessness.

PRECAUTIONS

If a rare sensitivity reaction occurs, the drug should be discontinued.

DIRECTIONS

Adults and Children 12 years of Age and Older: Two caplets, geltabs or gelcaps at bedtime or as directed by physician. Do not exceed recommended dosage. Not for use in children under 12 years of age.

WARNINGS

Do not use if carton is opened or printed neck wrap or printed foil inner seal is broken. Do not give to children under 12 years of age. If sleeplessness persists continuously for more than 2 weeks, consult your doctor. Insomnia may be a symptom of serious underlying medical illness. Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists, or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland. Avoid alcoholic beverages while taking this product. Do not take this product if your are taking sedatives or tranquilizers without first consulting your doctor.

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. Keep this and all drugs out of the reach of children. In case of accidental overdose, contact a doctor or poison control center immediately. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms. Do not use with other products containing acetaminophen.

ALCOHOL WARNING

For this and all other pain relievers, including aspirin, ibuprofen, ketoprofen and naproxen sodium, if you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take pain relievers.

CAUTION

This product will cause drowsiness. Do not drive a motor vehicle or operate machinery after use.

OVERDOSAGE INFORMATION

Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In adults and adolescents, hepatic toxicity has rarely been reported following ingestion of acute overdoses of less than 10 grams. Fatalities are infrequent (less than 3–4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children, an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion.

In adults and adolescents, regardless of the quantity of acetaminophen reported to have been ingested, administer acetylcysteine immediately if 24 hours or less have elapsed from the reported time of ingestion. For full prescribing information, refer to the acetylcysteine package insert. Do not await results of assays for plasma acetaminophen level before initiating treatment with acetylcysteine. The following additional procedures are recommended. The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. A plasma acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. If plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, acetylcysteine therapy should be continued. Liver function studies should be obtained initially and repeated at 24-hour intervals.

Serious toxicity or fatalities are extremely infrequent in children, possibly due to differences in the way they metabolize acetaminophen. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount was ingested, obtain a plasma acetaminophen level. The plasma acetaminophen level should be obtained as soon as possible, but no sooner than 4 hours following the ingestion. If the plasma level falls above the lower treatment line on the acetaminophen overdose nomogram, the acetylcysteine therapy should be initiated and continued for a full course of therapy. If plasma acetaminophen assay capability is not available, and the estimated acetaminophen ingestion exceeds 150 mg/kg, acetylcysteine therapy should be initiated and continued for a full course of therapy.

For additional emergency information, call your regional poison center or call the Rocky Mountain Poison Center toll-free, (1-800-525-6115).

Diphenhydramine toxicity should be treated as you would an antihistamine/anticholinergic overdose and is likely to be present within a few hours after acute ingestion.

ALCOHOL INFORMATION

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports almost invariably involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Professionals should alert their patients who regularly consume large amounts of alcohol not to exceed recommended doses of acetaminophen.

INACTIVE INGREDIENTS

Caplets: Cellulose, Cornstarch, Hydroxypropyl Methylcellulose, Magnesium Stearate or Stearic Acid and Colloidal Silicon Dioxide, Polyethylene Glycol, Polysorbate 80, Sodium Citrate, Sodium Starch Glycolate, Titanium Dioxide, Blue #1 and Blue #2.

Geltabs/Gelcaps: Benzyl Alcohol, Butylparaben, Castor Oil, Cellulose, Cornstarch, Edetate Calcium Disodium, Gelatin, Hydroxypropyl Methylcellulose, Magnesium Stearate, Propylparaben, Sodium Lauryl Sulfate, Sodium Citrate, Sodium Propionate, Sodium Starch Glycolate, Titanium Dioxide, Blue #1 and Red #28.

HOW SUPPLIED

Caplets (colored light blue imprinted "Tylenol PM") tamper-resistant bottles of 24, 50, 100, and 150.

Geltabs/Gelcaps (colored blue and white imprinted "TYLENOL PM") tamper-resistant bottles of 24 and 50.

Shown in Product Identification Guide, page 323

Maximum Strength

TYLENOL® SINUS

Geltabs, Gelcaps, Caplets and Tablets

DESCRIPTION

Each ***Maximum Strength TYLENOL® SINUS Geltab, Gelcap, Caplet or Tablet*** contains acetaminophen 500 mg, pseudoephedrine hydrochloride 30 mg.

ACTIONS

Maximum Strength TYLENOL® SINUS contains a proven analgesic-antipyretic and a decongestant. Maximum allowable non-prescription levels of acetaminophen pseudoephedrine provide temporary relief of sinus headache and congestion. Acetaminophen is equal to aspirin in analgesic and antipyretic effectiveness and it is unlikely to produce many of the side effects associated with aspirin and aspirin containing products.

Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center. Pseudoephedrine hydrochloride is a sympathomimetic amine which promotes sinus drainage by reducing nasopharyngeal mucosal congestion.

INDICATIONS

Maximum Strength TYLENOL® SINUS provides for the temporary relief of nasal and sinus congestion and pain and headaches. ***Maximum Strength TYLENOL® SINUS*** is particularly well-suited in patients with aspirin allergy, hemostatic disturbances (including anticoagulant therapy), and bleeding diatheses (e.g., hemophilia) and gastrointestinal disease (e.g., ulcer, gastritis, hiatus hernia).

PRECAUTIONS

If a rare sensitivity occurs, the drug should be discontinued. Although pseudoephedrine is virtually without pressor effect in normotensive patients, it should be used with caution in hypertensives.

DIRECTIONS

Adults and Children 12 years of Age and Older: Two Caplets, Gelcaps, or Geltabs every 4–6 hours. Do not exceed eight Tablets, Caplets, Gelcaps, or Geltabs in any 8 hour period. Not for use in children under 12 years of age.

WARNINGS

Do not use if carton is opened or if blister unit is broken or not take for pain for more than 7 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists. or get worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. **Do not exceed recommended dosage.** If nervousness, dizziness or sleeplessness occur, discontinue use and consult a doctor. Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor.

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. Keep this and all drugs out of the reach of children. In case of accidental overdose, contact a doctor or poison control center immediately. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms. Do not use with other products containing acetaminophen.

ALCOHOL WARNING

For this and all other pain relievers, including aspirin, ibuprofen, ketoprofen and naproxen sodium, if you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take pain relievers.

DRUG INTERACTION PRECAUTION

Do not use this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

OVERDOSAGE INFORMATION

Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In adults and adolescents, hepatic toxicity has rarely been reported following ingestion of acute overdoses of less than 10 grams. Fatalities are infrequent (less than 3–4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children, an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion.

In adults and adolescents, regardless of the quantity of acetaminophen reported to have been ingested, administer acetylcysteine immediately if 24 hours or less have elapsed

Medeva Pharmaceuticals, Inc.—Cont.

INDICATIONS AND USAGE
GASTROCROM is indicated in the management of patients with mastocytosis. Use of this product has been associated with improvement in diarrhea, flushing, headaches, vomiting, urticaria, abdominal pain, nausea, and itching in some patients.

CONTRAINDICATIONS
GASTROCROM is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium.

WARNINGS
The recommended dosage should be decreased in patients with decreased renal or hepatic function. Severe anaphylactic reactions may occur rarely in association with cromolyn sodium administration.

PRECAUTIONS
In view of the biliary and renal routes of excretion of GASTROCROM, consideration should be given to decreasing the dosage of the drug in patients with impaired renal or hepatic function.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies of cromolyn sodium in mice (12 months intraperitoneal administration at doses up to 150 mg/kg three days per week), hamsters, (intraperitoneal administration at doses up to 52.6 mg/kg three days per week for 15 weeks followed by 17.5 mg/kg three days per week for 37 weeks), and rats (18 months subcutaneous administration at doses up to 75 mg/kg six days per week) showed no neoplastic effects. The average daily maximum dose levels administered in these studies were 192.9 mg/m^2 for mice, 47.2 mg/m^2 for hamsters and 385.8 mg/m^2 for rats. These doses correspond to 13%, 3.2%, and 26% of the maximum daily human dose of 1480 mg/m^2.

Cromolyn sodium showed no mutagenic potential in Ames Salmonella/microsome plate assays, mitotic gene conversion in *Saccharomyces cerevisiae* and in an *in vitro* cytogenetic study in human peripheral lymphocytes.

No evidence of impaired fertility was shown in laboratory reproduction studies conducted subcutaneously in rats at the highest doses tested, 175 mg/kg/day (1050 mg/m^2) in males and 100 mg/kg/day (600 mg/m^2) in females. Theses doses are approximately 71% and 41% of the maximum daily human dose, respectively, based on mg/m^2.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered subcutaneously to pregnant mice and rats at maximum daily dose of 540 mg/kg (1620 mg/m^2) and 164 mg/kg (984 mg/m^2), respectively, and intravenously to rabbits at a maximum daily doses of 485 mg/kg (5820 mg/m^2) produced no evidence of fetal malformations. These doses represent 109%, 66% and 393%, respectively, of the maximum daily human dose on a mg/m^2 basis. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GASTROCROM is administered to a nursing woman.

Pediatric Use: Animal studies suggest increased risk of toxicity in premature animals when given doses much higher than clinically recommended. In term infants up to six months of age, available clinical data suggest that the dose should not exceed 20 mg/kg/day. The use of this product in pediatric patients less than two years of age should be reserved for patients with severe disease in which the potential benefits clearly outweigh the risks.

ADVERSE REACTIONS
Most of the adverse events reported in mastocytosis patients have been transient and could represent symptoms of the disease. The most frequently reported adverse events in mastocytosis patients who have received GASTROCROM during clinical studies were headache and diarrhea, each of which occurred in 4 of the 87 patients. Pruritus, nausea, and myalgia were each reported in 3 patients and abdominal pain, rash, and irritability in 2 patients each. One report of malaise was also recorded.

Other Adverse Events: Additional adverse events have been reported during studies in other clinical conditions and from worldwide postmarketing experience. In most cases the available information is incomplete and attribution to the drug cannot be determined. The majority of these reports involve the gastrointestinal system and include: diarrhea, nausea, abdominal pain, constipation, dyspepsia, flatulence, glossitis, stomatitis, vomiting, dysphagia, esophagospasm. Other less commonly reported events (the majority representing only a single report) include the following:

Skin:	pruritus, rash, urticaria/angioedema, erythema/burning, photosensitivity
Musculoskeletal:	arthralgia, myalgia, stiffness/weakness of legs
Neurologic:	headache, dizziness, hypoesthesia, paresthesia, migraine, convulsions, flushing
Psychiatric:	psychosis, anxiety, depression, hallucinations, behavior change, insomnia, nervousness
Heart Rate:	tachycardia, premature ventricular contractions (PVCs), palpitations
Respiratory:	pharyngitis, dyspnea
Miscellaneous:	fatigue, edema, unpleasant taste, chest pain, postprandial lightheadedness and lethargy, dysuria, urinary frequency, purpura, hepatic function test abnormal, polycythemia, neutropenia, pancytopenia, tinnitus, lupus erythematosus (LE) syndrome

DOSAGE AND ADMINISTRATION
NOT FOR INHALATION OR INJECTION. SEE DIRECTIONS FOR USE.

The usual starting dose is as follows:

Adults (13 Years and Older): Two ampules four times daily, taken one-half hour before meals and at bedtime.

Children 2–12 Years: One ampule four times daily, taken one-half hour before meals and at bedtime.

Pediatric Patients Under 2 Years: Not recommended.

If satisfactory control of symptoms is not achieved within two to three weeks, the dosage may be increased but should not exceed 40 mg/kg/day.

Patients should be advised that the effect of GASTROCROM therapy is dependent upon its administration at regular intervals, as directed.

Maintenance Dose: Once a therapeutic response has been achieved, the dose may be reduced to the minimum required to maintain the patient with a lower degree of symptomatology. To prevent relapses, the dosage should be maintained.

Administration: GASTROCROM should be administered as a solution at least $^1/_2$ hour before meals and at bedtime after preparation according to the following directions:

1. Break open ampule(s) and squeeze liquid contents of ampule(s) into a glass of water.
2. Stir solution.
3. Drink all of the liquid.

HOW SUPPLIED
GASTROCROM Oral Concentrate is an unpreserved, colorless solution supplied in a low density polyethylene plastic unit-dose ampule with 8 ampules per foil pouch. Each 5 mL ampule contains 100 mg cromolyn sodium, USP, in purified water.

NDC 53014-678-70 96 ampules × 5 mL

GASTROCROM Oral Concentrate should be stored between 15°–30°C (59°–86°F) and protected from light. Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children.

Store ampules in foil pouch until ready for use.

CAUTION: Federal law prohibits dispensing without prescription.

Marketed by:
MEDEVA PHARMACEUTICALS
Medeva Pharmaceuticals, Inc.
Fort Worth, TX 76155

Manufactured by:
Automatic Liquid Packaging, Inc.
Woodstock, IL 60098 USA
®FISONS plc

7/96
R081B

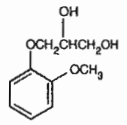
℞ HUMIBID® L.A. Tablets
GUAIFENESIN

HUMIBID® Pediatric Capsules
GUAIFENESIN

HUMIBID® DM Tablets
GUAIFENESIN/DEXTROMETHORPHAN HYDROBROMIDE

DESCRIPTION
HUMIBID® L.A. Tablets: Each light green, scored, sustained-release tablet provides 600 mg guaifenesin. Inactive ingredients: Dibasic calcium phosphate, ethylcellulose, FD & C Blue #1 Lake, D & C Yellow #10 Lake, magnesium stearate, sodium lauryl sulfate, stearic acid.

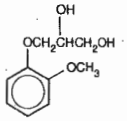
Chemically, guaifenesin is 3-(2-methoxyphenoxy)-1, 2-propanediol and has the following structural formula:



$C_{10}H_{14}O_4$ MW=198.22

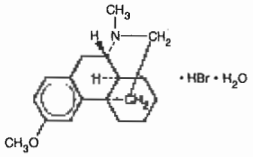
HUMIBID® Pediatric Capsules: Each green and clear capsule provides 300 mg guaifenesin in a sustained-release formulation intended for oral administration. The microencapsulated contents of a capsule may be sprinkled on a small amount of soft food immediately prior to ingestion, making the product ideal for pediatric patients and other patients unable to swallow capsules or tablets. Capsules are oversized to facilitate opening but may also be swallowed whole.

HUMIBID® DM Tablets: Each dark green, scored, sustained-release tablet provides 600 mg guaifenesin and 30 mg dextromethorphan hydrobromide. Inactive ingredients: Dibasic calcium phosphate, stearic acid, FD & C Blue #1 Lake, D & C Yellow #10 Lake, sodium lauryl sulfate, ethylcellulose, magnesium stearate. Chemically, guaifenesin is 3-(2-methoxyphenoxy)-1,2-propanediol and has the following structural formula:



$C_{10}H_{14}O_4$ MW=198.00

Dextromethorphan hydrobromide is a salt of the methyl ether of the dextrorotatory isomer of levorphanol, a narcotic analgesic. Chemically, it is 3-methoxy-17-methyl-9α, 13α, 14α-morphinan hydrobromide monohydrate and has the following structural formula:



$C_{18}H_{25}NO \cdot HBr \cdot H_2$ MW=370.33

CLINICAL PHARMACOLOGY
Guaifenesin is an expectorant which increases respiratory tract fluid secretions and helps to loosen phlegm and bronchial secretions. By reducing the viscosity of secretions, guaifenesin increases the efficiency of the mucociliary mechanism in removing accumulated secretions from the upper and lower airway. Guaifenesin is readily absorbed from the gastrointestinal tract and is rapidly metabolized and excreted in the urine. Guaifenesin has a plasma half-life of one hour. The major urinary metabolite is β-(2-methoxyphenoxy) lactic acid.

Dextromethorphan is an antitussive agent which, unlike the isomeric levorphanol, has no analgesic or addictive properties. The drug acts centrally and elevates the threshold for coughing. It is about equal to codeine in depressing the cough reflex. In therapeutic dosage, dextromethorphan does not inhibit ciliary activity. Dextromethorphan is rapidly absorbed from the gastrointestinal tract, metabolized by the liver and excreted primarily in the urine.

INDICATIONS AND USAGE
HUMIBID® L.A. Tablets and **HUMIBID® Pediatric Capsules** are indicated for the temporary relief of coughs associated with respiratory tract infections and related conditions such as sinusitis, pharyngitis and bronchitis, and asthma, when these conditions are complicated by tenacious mucus and/or mucus plugs and congestion.

HUMIBID® DM Tablets are indicated for the temporary relief of coughs associated with upper respiratory tract infections and related conditions such as sinusitis, pharyngitis and bronchitis, particularly when these conditions are complicated by tenacious mucus and/or mucus plugs and congestion.

HUMIBID® L.A. Tablets, HUMIBID® Pediatric Capsules and HUMIBID® DM Tablets are effective in productive as well as non-productive cough, but are of particular value in dry, non-productive cough which tends to injure the mucous membrane of the air passages.

CONTRAINDICATIONS

HUMIBID® L.A. Tablets and HUMIBID® Pediatric Capsules: These products are contraindicated in patients with hypersensitivity to guaifenesin.

HUMIBID® DM Tablets:
This drug is contraindicated in patients with hypersensitivity to guaifenesin or dextromethorphan and in patients receiving monoamine oxidase inhibitor (MAOI) therapy and for 14 days after stopping MAOI therapy. (See **Drug Interactions** section).

PRECAUTIONS

General: Before prescribing medication to suppress or modify cough, it is important that the underlying cause of cough is identified, that modification of cough does not increase the risk of clinical or physiological complications, and that appropriate therapy for the primary disease is instituted.
Dextromethorphan should be used with caution in sedated or debilitated patients, and in patients to be confined to the supine position.

Drug Interactions: HUMIBID® DM Tablets: Do not prescribe this product for use in patiente that are now taking a prescription MAOI (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 14 days after stopping the MAOI drug therapy.

Drug/Laboratory Test Interactions: Guaifenesin may increase renal clearance for urate and thereby lower serum uric acid levels. Guaifenesin may produce an increase in urinary 5-hydroxyindoleacetic acid and may therefore interfere with the interpretation of this test for the diagnosis of carcinoid syndrome. It may also falsely elevate the VMA test for catechols. Administration of these products should be discontinued 48 hours prior to the collection of urine specimens for such tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No data are available on the long-term potential of guaifenesin or of dextromethorphan for carcinogenesis, mutagenesis, or impairment of fertility in animals or humans.

Pregnancy: Category C: Animal reproduction studies have not been conducted with guaifenesin or with dextromethorphan. It is also not known whether these drugs can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, these products should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether guaifenesin or dextromethorphan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when these products are administered to a nursing mother and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

No serious side effects from guaifenesin or dextromethorphan have been reported.

OVERDOSAGE

Overdosage with guaifenesin is unlikely to produce toxic effects since its toxicity is low. Guaifenesin, when administered by stomach tube to test animals in doses up to 5 grams/kg, produced no signs of toxicity. In severe cases of overdosage, treatment should be aimed at reducing further absorption of the drug. Gastric emptying (Syrup of Ipecac) and/or lavage is recommended as soon as possible after ingestion.
Overdosage with dextromethorphan may produce central excitement and mental confusion. Very high doses may produce respiratory depression. One case of toxic psychosis (hyperactivity, marked visual and auditory hallucinations) after ingestion of a single 300 mg dose of dextromethorphan has been reported.

DOSAGE AND ADMINISTRATION

HUMIBID® L.A. Tablets: Adults and adolescents over 12 years of age: One or two tablets every 12 hours not to exceed 4 tablets (2400 mg) in 24 hours. Children 6 to 12 years: One tablet every 12 hours not to exceed 2 tablets (1200 mg) in 24 hours. Children 2 to 6 years: $^1/_2$ tablet every 12 hours not to exceed 1 tablet (600 mg) in 24 hours.

HUMIBID® DM Tablets: Adults and adolescents over 12 years of age: One or two tablets every 12 hours not to exceed 4 tablets in 24 hours. Children 6 to 12 years: One tablet every 12 hours not to exceed 2 tablets in 24 hours. Children 2 to 6 years: $^1/_2$ tablet every 12 hours not to exceed 1 tablet in 24 hours.

HUMIBID® Pediatric Capsules: Adults and adolescents over 12 years of age: Two to four capsules every 12 hours not to exceed 8 capsules in 24 hours. Children 6 to 12 years: Two capsules every 12 hours not to exceed 4 capsules in 24 hours. Children 2 to 6 years: One capsule every 12 hours not to exceed 2 capsules in 24 hours.

HOW SUPPLIED

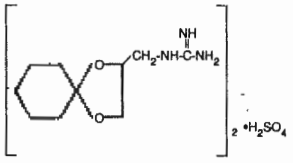
HUMIBID® L.A. Tablets: Bottles of 100 tablets (NDC 53014-012-10) and 500 tablets (NDC 53014-012-50). Light green, scored tablets are embossed with "Adams/012".
HUMIBID® Pediatric Capsules: Bottles of 100 capsules (NDC 53014-402-10). White beads in a green and clear capsule imprinted with "Adams/402".
HUMIBID® DM Tablets: Bottles of 100 tablets (NDC 53014-030-10) and 500 tablets (NDC 53014-030-50). Dark green, scored tablets are embossed with "Adams/030."
CAUTION: Federal law prohibits dispensing without prescription.
HUMIBID® L.A. Tablets:
August 1995
HUMIBID® DM Tablets:
August 1995
HUMIBID® Pediatric Capsules
August 1995

HYLOREL® Tablets

[hi'lō-rel'']
(guanadrel sulfate tablets, USP)
Rev. 7/96
R253A
814 438 104

DESCRIPTION

HYLOREL Tablets for oral administration contain guanadrel sulfate, an antihypertensive agent belonging to the class of adrenergic neuron blocking drugs. Guanadrel sulfate is (1,4-Dioxaspiro[4.5] dec-2-ylmethyl) guanidine sulfate with a molecular weight of 524.63. The empirical formula is $(C_{10}H_{19}N_3O_2)_2 \cdot H_2SO_4$. It is a white to off-white crystalline powder, which melts with decomposition at about 235°C. It is soluble in water to the extent of 76 mg/mL.
The structural formula is:



HYLOREL Tablets are available in two strengths: 10 mg and 25 mg. Inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, microcrystalline cellulose and talc. The 10 mg tablet also contains FD&C Yellow No. 6.

CLINICAL PHARMACOLOGY

Guanadrel sulfate is an orally effective antihypertensive agent that lowers both systolic and diastolic arterial blood pressures. Guanadrel sulfate inhibits sympathetic vasoconstriction by inhibiting norepinephrine release from neuronal storage sites in response to stimulation of the nerve and also causes depletion of norepinephrine from the nerve ending. This results in relaxation of vascular smooth muscle which decreases total peripheral resistance, and decreases venous return, both of which reduce the ability to maintain blood pressure in the upright position. The result is a hypotensive effect that is greater in the standing than in the supine position by about 10 mmHg systolic and 3.5 mmHg diastolic, on the average. Heart rate is also decreased usually by about 5 beats/minute. Fluid retention occurs during treatment with guanadrel, particularly when it is not accompanied by a diuretic. The drug does not inhibit parasympathetic nerve function nor does it enter the central nervous system.
Guanadrel sulfate is rapidly absorbed after oral administration. Plasma concentrations generally peak $1^1/_2$ to 2 hours after ingestion. The half-life is about 10 hours, but individual variability is great. Approximately 85% of the drug is eliminated in the urine. Urinary excretion is approximately 85% complete within 24 hours after administration; about 40% of the dose is excreted as unchanged drug. The disposition of guanadrel sulfate is significantly altered in patients with impaired renal function. A study in such patients has shown that as renal function (measured as creatinine clearance) declines, apparent total blody clearance, renal and apparent nonrenal clearances decrease, and the terminal elimination half-life is prolonged. Dosage adjustments may be necessary, especially in patients with creatinine clearances of less than 60 mL/min (see DOSAGE AND ADMINISTRATION).
Guanadrel sulfate begins to decrease blood pressure within two hours and produces maximal decreases in four to six hours. No significant change in cardiac output accompanies the blood pressure decline in normal individuals.
Because drugs of the adrenergic neuron blocking class are transported into the neuron by the "norepinephrine pump", drugs that compete for the pump may block their effects. Tricyclic antidepressants have been shown to block the norepinephrine-depleting effect of guanadrel sulfate in rats and monkeys, and the blood pressure lowering effect of guanadrel sulfate in monkeys. Similar effects have been seen with guanethidine and inhibition of the antihypertensive effects of guanadrel sulfate by tricyclic antidepressants in humans should be presumed.
Therefore caution is recommended if guanadrel sulfate and a tricyclic antidepressant are used concomitantly. Should patients be on both a tricyclic antidepressant and guanadrel sulfate, caution is advised upon discontinuation of the tricyclic antidepressant, especially if discontinued abruptly, as an enhanced effect of guanadrel sulfate may occur.
Chlorpromazine seems to have a similar effect on guanethidine and may affect guanadrel as well. Indirectly acting adrenergic amines are transported into the neuron by the "norepinephrine pump" and may interfere with uptake or may displace blocking agents. Ephedrine rapidly reverses the effects of guanadrel but other agents have not been studied.
Agents of the guanethidine class cause increased sensitivity to circulating norepinephrine, probably by preventing uptake of norepinephrine by adrenergic neurons, the usual mechanism for terminating norepinephrine effects. Agents of this class are thus dangerous in the presence of excess norepinephrine, e.g., in the presence of a pheochromocytoma.
In controlled clinical studies comparing guanadrel to guanethidine and methyldopa, involving about 2000 patients exposed to guanadrel, patients with initial supine blood pressures averaging 160–170/105–110 mmHg had decreases in blood pressure of 20–25/15–20 mmHg in the standing position. The decreases in supine blood pressure were less than the decreases in standing blood pressure by 6–10/2–7 mmHg in different studies. Guanethidine and guanadrel were very similar in effectiveness while methyldopa had a larger effect on supine systolic pressure. Side effects of guanadrel and guanethidine were generally similar in type (see ADVERSE REACTIONS) while methyldopa had more central nervous system effects (depression, drowsiness) but fewer orthostatic effects and less diarrhea.

INDICATIONS AND USAGE

HYLOREL Tablets are indicated for the treatment of hypertension in patients not responding adequately to a thiazide type diuretic. HYLOREL should be added to a diuretic regimen for optimum blood pressure control.

CONTRAINDICATIONS

HYLOREL Tablets are contraindicated in known or suspected pheochromocytoma.
HYLOREL should not be used concurrently with, or within one week of, monoamine oxidase inhibitors.
HYLOREL should not be used in patients hypersensitive to the drug.
HYLOREL should not be used in patients with frank congestive heart failure.

WARNINGS

a. Orthostatic Hypotension

Orthostatic hypotension and its consequences (dizziness and weakness) are frequent in people treated with HYLOREL Tablets. Rarely, fainting upon standing or exercise is seen. Careful instructions to the patient can minimize these symptoms, as can recognition by the physician that the supine blood pressure does not constitute an adequate assessment of the effects of this drug. Patients with known regional vascular disease (cerebral, coronary) are at particular risk from marked orthostatic hypotension and HYLOREL should be avoided in them unless drugs with lesser degrees of orthostatic hypotension are ineffective or unacceptable. In such patients hypotensive episodes should be avoided, even if this requires accepting a poorer degree of blood pressure control.
Instructions to patients: Patients should be advised about the risk of orthostatic hypotension and told to sit or lie down immediately at the onset of dizziness or weakness so that they can prevent loss of consciousness. They should be told that postural hypotension is worst in the morning and upon arising, and may be exaggerated by alcohol, fever, hot weather, prolonged standing, or exercise.
Surgery: To reduce the possibility of vascular collapse during anesthesia, guanadrel should be discontinued 48–72 hours before elective surgery. If emergency surgery is required, the anesthesiologist should be made aware that the patient has been taking HYLOREL and that preanesthetic and anesthetic agents should be administered cautiously in reduced dosage. If vasopressors are needed they must be used

Continued on next page

...ion and circulatory collapse. Severe hypokalemia ...can occur, probably due to a compartmental shift rather than a depletion of potassium. No organ damage or significant metabolic derangement is associated with pseudoephedrine overdosage. Overdosage with guaifenesin is unlikely to produce toxic effects since its toxicity is much lower than that of pseudoephedrine. In severe cases of overdosage, it is recommended to monitor the patient in an intensive care setting.

LD_{50} of pseudoephedrine (single oral dose) has been reported to be 726 mg/kg in the mouse, 2206 mg/kg in the rat and 1177 mg/kg in the rabbit. The toxic and lethal concentrations in human biologic fluids are not known. Urinary excretion increases with acidification and decreases with alkalization of the urine. There are few published reports of toxicity due to pseudoephedrine and no case of fatal overdosage has been reported. Guaifenesin, when administered by stomach tube to test animals in doses up to 5 grams/kg, produced no signs of toxicity.

...the action of sustained release products may continue ...long as 12 hours, treatment of overdosage should be ...d toward reducing further absorption and supporting ...patient for at least that length of time. Gastric emptying ...of Ipecac) and/or lavage is recommended as soon as ...ble after ingestion, even if the patient has vomited spontaneously. Either isotonic or half-isotonic saline may be used for lavage. Administration of an activated charcoal slurry is beneficial after lavage and/or emesis if less than 4 hours have passed since ingestion. Saline cathartics, such as Milk of Magnesia, are useful for hastening the evacuation of unabsorbed medication.

...energic receptor blocking agents are antidotes to pseudoephedrine. In practice, the most useful is the beta-blocker propranolol which is indicated when there are signs of cardiac toxicity. Theoretically, pseudoephedrine is dialyzable but procedures have not been clinically established.

DOSAGE AND ADMINISTRATION

Adults and adolescents over 12 years of age: 1 or 2 dark blue A.M. tablet(s) in the morning and 1 or 2 light green P.M. tablet(s) 12 hours later. Repeat A.M. and P.M. dosing cycle every 12 hours for 14 days.

Tablets should not be crushed or chewed prior to swallowing.

HOW SUPPLIED

NDC 53014-308-14 SYN-Rx 14 Day Treatment Regimen, is available as a shelf-pak consisting of three 14 Day Treatment Regimen packs. Each 14 Day Treatment Regimen contains sustained-release tablets as follows:

NDC 53014-017, 28 dark blue elongated and scored A.M. tablets embossed with "Adams/017", each containing 60 mg pseudoephedrine HCl and 600 mg guaifenesin.

NDC 53014-012, 28 light green elongated and scored P.M. tablets embossed with "Adams/012", each containing 600 mg guaifenesin.

Store at controlled room temperature between 15°C and 30°C (59°F–86°F).

Dispensed as a complete 14 day pack.

Caution: Federal law prohibits dispensing without prescription.

...1996

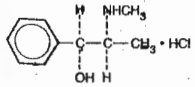
SYN™-Rx DM Tablets ℞
14 Day Treatment Regimen

DESCRIPTION

Each SYN-Rx DM 14 Day Treatment Regimen pack of 56 tablets consists of two different drug treatment phases as follows: an **A.M. Treatment Phase** comprised of 28 light blue scored controlled-release tablets, each containing 60 mg pseudoephedrine HCl and 600 mg guaifenesin, embossed with "Adams/310"; and a **P.M. Treatment Phase** comprised of 28 yellow scored controlled-release tablets, each containing 30 mg dextromethorphan hydrobromide and 600 mg guaifenesin, embossed with "Adams/309".

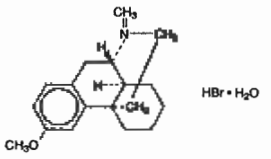
SYN-Rx DM 14 Day Treatment Regimen contains ingredients of three therapeutic classes: nasal decongestant, antitussive, and expectorant.

Pseudoephedrine hydrochloride is a nasal decongestant. Chemically, it is [S-(R*,R*)]-α-[1-(methylamino)ethyl] benzenemethanol hydrochloride and has the following structural formula:



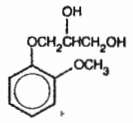
Molecular weight = 201.70;
chemical formula = $C_{10}H_{15}NO \cdot HCl$

Dextromethorphan hydrobromide is a salt of the methyl ether of the dextrorotatory isomer of levorphanol, a narcotic analgesic. Chemically, it is 3-methoxy-17-methyl-9α, 13α, 14α - morphinan hydrobromide monohydrate and has the following structural formula:



$C_{18}H_{25}NO \cdot HBr \cdot H_2O$ MW = 370.33

Guaifenesin is an expectorant. Chemically, it is 3-(2-methoxyphenoxy)-1, 2-propanediol and has the following structural formula:



Molecular weight = 198.22; chemical formula = $C_{10}H_{14}O_4$

Inactive Ingredients: Each light blue A.M. tablet and yellow P.M. tablet contains stearic acid, dibasic calcium phosphate, sodium lauryl sulfate, ethylcellulose, magnesium stearate. Each light blue A.M. tablet also contains FD&C Blue #1 Aluminum Lake. Each yellow P.M. tablet also contains D & C Yellow #10 Lake.

CLINICAL PHARMACOLOGY

Pseudoephedrine hydrochloride is an orally indirect acting sympathomimetic amine and exerts a decongestant action on the nasal mucosa. It does this by vasoconstriction which results in reduction of tissue hyperemia, edema, nasal congestion, and an increase in nasal airway patency. In the usual dose it has minimal vasopressor effects. Pseudoephedrine is rapidly and almost completely absorbed from the gastrointestinal tract. It has a plasma half-life of 6 to 8 hours. Alkaline urine is associated with slower elimination of the drug. The drug is distributed to body tissues and fluids, including the central nervous system (CNS). Approximately 50% to 75% of the administered dose is excreted unchanged in the urine; the remainder is apparently metabolized in the liver to inactive compounds by N-demethylation, parahydroxylation and oxidative deamination.

Dextromethorphan is an antitussive agent which, unlike the isomeric levorphanol, has no analgesic or addictive properties. The drug acts centrally and elevates the threshold for coughing. It is about equal to codeine in depressing the cough reflex. In therapeutic dosage, dextromethorphan does not inhibit ciliary activity. Dextromethorphan is rapidly absorbed from the gastrointestinal tract, metabolized by the liver and excreted primarily in the urine.

Guaifenesin is an expectorant which increases respiratory tract fluid secretions and helps to loosen phlegm, bronchial and nasal secretions. By reducing the viscosity of secretions, guaifenesin increases the efficiency of the mucociliary mechanism in removing accumulated secretions from the upper and lower airway. Guaifenesin is readily absorbed from the gastrointestinal tract and is rapidly metabolized and excreted in the urine. Guaifenesin has a plasma half-life of one hour. The major urinary metabolite is β-(2-methoxyphenoxy) lactic acid.

INDICATIONS AND USAGE

SYN-Rx DM 14 Day Treatment Regimen is indicated for the temporary relief of nasal congestion and cough associated with respiratory tract infections and related conditions such as sinusitis, bronchitis, and asthma, when these conditions are complicated by tenacious mucus, and/or mucus plugs and congestion. In the treatment of bacterial sinusitis this treatment regimen may be used concomitantly with appropriate antibiotic therapy. The product is effective in productive as well as nonproductive cough, but is of particular value in dry, nonproductive cough which tends to injure the mucous membrane of the air passages.

CONTRAINDICATIONS

This product is contraindicated in patients with hypersensitivity to guaifenesin, dextromethorphan HBr, or psuedoephedrine HCl, or with hypersensitivity or idiosyncrasy to sympathomimetic amines which may be manifested by insomnia, dizziness, weakness, tremor or arrhythmias.

Sympathomimetic amines are contraindicated in patients with severe hypertension and severe coronary artery disease.

The product is contraindicated in patients on monoamine oxidase inhibitor (MAOI) therapy and for 14 days after stopping MAOI therapy. (see **Drug Interaction** section).

WARNINGS

Sympathomimetic amines should be used with caution in patients with hypertension, ischemic heart disease, diabetes mellitus, increased intraocular pressure, hyperthyroidism, or prostatic hypertrophy. Sympathomimetics may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension. **Do not exceed recommended dosage.**

Do not prescribe this product for use in patients that are now taking a prescription MAOI (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 14 days after stopping the MAOI drug therapy.

Hypertensive crises can occur with concurrent use of pseudoephedrine and monoamine oxidase inhibitors (MAOI), and for 14 days after stopping the MAOI drug therapy, indomethacine, or with beta-blockers and methyldopa. If a hypertensive crisis occurs, these drugs should be discontinued immediately and therapy to lower blood pressure should be instituted. Fever should be managed by means of external cooling.

PRECAUTIONS

General: Use with caution in patients with diabetes, hypertenson, cardiovascular disease and intolerance to ephedrine.

Before prescribing medication to suppress or modify cough, it is important that the underlying cause of cough is identified, that modification of cough does not increase the risk of clinical or physiological complications, and that appropriate therapy for the primary disease is instituted.

Dextromethorphan should be used with caution in sedated or debilitated patients, and in patients confined to the supine position.

Failure of symptoms to completely resolve should alert the patient and physician that further diagnostic studies are indicated.

Pediatric Use: This product is not recommended for use in pediatric patients under 12 years of age.

Use in Elderly: The elderly (60 years and older) are more likely to experience adverse reactions to sympathomimetics. Overdosage of sympathomimetics in this age group may cause hallucinations, convulsions, CNS depression and death.

Drug Interactions: Do not prescribe this product for use in patients that are now taking a monoamine oxidase inhibitor (MAOI) drug (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease) or for 14 days after stopping the MAOI drug therapy. Beta-adrenergic blockers and inhibitors (MAOI) may potentiate the pressor effect of pseudoephedrine. Concurrent use of digitalis glycosides may increase the possibility of cardiac arrhythmias. Sympathomimetics may reduce the hypotensive effects of guanethidine, mecamylamine, methyldopa, reserpine and veratrum alkaloids. Concurrent use of tricyclic antidepressants may antagonize the effects of pseudoephedrine.

Drug/Laboratory Test Interactions: Guaifenesin may increase renal clearance for urate and thereby lower serum uric acid levels. Guaifenesin may produce and increase in urinary 5-hydroxyindoleacetic acid and may therefore interfere with the interpretation of this test for the diagnosis of carcinoid syndrome. It may also falsely elevate the VMA test for catechols. Administration of this drug should be discontinued 48 hours prior to the collection of urine specimens for such tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No data are available on the long-term potential of the components of this product for carcinogenesis, mutagenesis, or impairment of fertility in animals or humans.

Pregnancy Category C: Animal reproduction studies have not been conducted with Syn-Rx DM Tablets. It is also not known whether Syn-Rx DM Tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Syn-Rx DM Tablets should be given to pregnant woman only if clearly needed.

Nursing Mothers: Pseudoephedrine is excreted in breast milk. Use of this product by nursing mothers is not recommended because of the higher than usual risk for pediatric patients from sympathomimetic amines.

ADVERSE REACTIONS

Some individuals may display sympathomimetic amine effects such as tachycardia, palpitations, headache, dizziness or nausea. Sympathomimetics have been associated with certain untoward reactions including fear, anxiety, nervousness, restlessness, tremor, weakness, pallor, respiratory difficulty, dysuria, insomnia, hallucinations, convulsions, CNS depression, arrhythmias, and cardiovascular collapse with hypotension. No serious side effects have been reported with the use of guaifenesin or dextromethorphan HBr.

Continued on next page

Medeva Pharmaceuticals, Inc.—Cont.

OVERDOSAGE

Since SYN-Rx DM 14 Day Treatment Regimen contains three pharmacologically different compounds, treatment of overdosage should be based upon the symptomatology of the patient as it relates to the individual ingredients. Treatment of acute overdosage would probably be based upon treating the patient for pseudoephedrine toxicity which may manifest itself as excessive CNS stimulation resulting in excitement, tremor, restlessness, and insomnia. Other effects may include tachycardia, hypertension, pallor, mydriasis, hyperglycemia and urinary retention. Severe overdosage may cause tachypnea or hypernea, hallucinations, convulsions, or delirium, but in some individuals there may be CNS depression with somnolence, stupor or respiratory depression. Arrhythmias (including ventricular fibrillation) may lead to hypotension and circulatory collapse. Severe hypokalemia can occur, probably due to a compartmental shift rather than a depletion of potassium. No organ damage or significant metabolic derangement is associated with pseudoephedrine overdosage. Overdosage with guaifenesin is unlikely to produce toxic effects since its toxicity is much lower than that of pseudoephedrine. In severe cases of overdosage, it is recommended to monitor the patient in an intensive care setting.

The LD_{50} of pseudoephedrine (single oral dose) has been reported to be 726 mg/kg in the mouse, 2206 mg/kg in the rat and 1177 mg/kg in the rabbit. The toxic and lethal concentrations in human biologic fluids are not known. Urinary excretion increases with acidification and decreases with alkalinization of the urine. There are few published reports of toxicity due to pseudoephedrine and no case of fatal overdosage has been reported. Guaifenesin, when administered by stomach tube to test animals in doses up to 5 grams/kg, produced no signs of toxicity.

Overdosage with dextromethorphan may produce central excitement and mental confusion. Very high doses may produce respiratory depression. One case of toxic psychosis (hyperactivity, marked visual and auditory hallucinations) after ingestion of a single 300 mg dose of dextromethorphan has been reported.

Since the action of sustained release products may continue for as long as 12 hours, treatment of overdosage should be directed toward reducing further absorption and supporting the patient for at least that length of time. Gastric emptying (Syrup of Ipecac) and/or lavage is recommended as soon as possible after ingestion, even if the patient has vomited spontaneously. Either isotonic or half-isotonic saline may be used for lavage. Administration of an activated charcoal slurry is beneficial after lavage and/or emesis if less than 4 hours have passed since ingestion. Saline cathartics, such as Milk of Magnesia, are useful for hastening the evacuation of unreleased medication.

Adrenergic receptor blocking agents are antidotes to pseudoephedrine. In practice, the most useful is the beta-blocker propranolol which is indicated when there are signs of cardiac toxicity. Theoretically, pseudoephedrine is dialyzable but procedures have not been clinically established.

DOSAGE AND ADMINISTRATION

Adults and adolescents over 12 years of age: 1 or 2 light blue A.M. tablets in the morning and 1 or 2 yellow P.M. tablets 12 hours later. Repeat A.M. and P.M. dosing cycle every 12 hours for 14 days. **Do not crush or chew tablets prior to swallowing.**

HOW SUPPLIED

NDC 53014-311-14 SYN-Rx DM 14 Day Treatment Regimen, containing 56 controlled-release tablets as follows:

NDC 53014-310, 28 light blue elongated and scored A.M. tablets embossed with "Adams/310", each containing 60 mg pseudoephedrine HCl and 600 mg guaifenesin;

NDC 53014-309, 28 yellow elongated and scored P.M. tablets embossed with "Adams/309", each containing 30 mg dextromethorphan HBr and 600 mg guaifenesin.

Store at controlled room temperature between 15°C and 30°C (59°F–86°F).

Dispense as a complete 14 day pack.

Caution: Federal law prohibits dispensing without prescription.

January 1996

TUSSIONEX®

Pennkinetic®

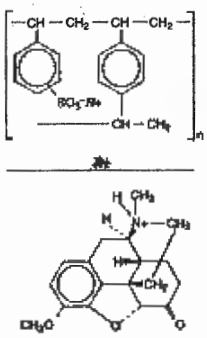
[tus'e-uh-nex]

(hydrocodone polistirex
[Warning: May be habit forming]
and chlorpheniramine polistirex)
Extended-Release Suspension
R 240G
Rev. 7/96

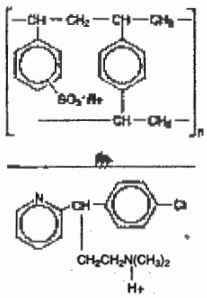
DESCRIPTION

Each teaspoonful (5 mL) of TUSSIONEX Pennkinetic Extended-Release Suspension contains hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate (Warning: May be habit-forming) and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate. TUSSIONEX Pennkinetic Extended-Release Suspension provides up to 12-hour relief per dose. Hydrocodone is a centrally-acting narcotic antitussive. Chlorpheniramine is an antihistamine. TUSSIONEX Pennkinetic Extended-Release Suspension is for oral use only.

Hydrocodone Polistirex: sulfonated styrene-divinylbenzene copolymer complex with 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one.



Chlorpheniramine Polistirex: sulfonated styrene-divinylbenzene copolymer complex with 2-[*p*-chloro-α-[2-(dimethylamino)ethyl]-benzyl]pyridine.



Inactive Ingredients: Ascorbic acid, D&C Yellow No. 10, ethylcellulose, FD&C Yellow No. 6, flavor, high fructose corn syrup, methylparaben, polyethylene glycol 3350, polysorbate 80, pregelatinized starch, propylene glycol, propylparaben, purified water, sucrose, vegetable oil, xanthan gum.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. The effects of hydrocodone in therapeutic doses on the cardiovascular system are insignificant. Hydrocodone can produce miosis, euphoria, physical and psychological dependence.

Chlorpheniramine is an antihistamine drug (H_1 receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Hydrocodone release from TUSSIONEX Pennkinetic Extended-Release Suspension is controlled by the Pennkinetic System, an extended-release drug delivery system which combines an ion-exchange polymer matrix with a diffusion rate-limiting permeable coating. Chlorpheniramine release is prolonged by use of an ion-exchange polymer system.

Following multiple dosing with TUSSIONEX Pennkinetic Extended-Release Suspension, hydrocodone mean peak plasma concentrations of 22.8 (5.9) ng/mL occurred at 3.4 hours. Chlorpheniramine mean (S.D.) peak plasma concentrations of 58.4 (14.7) ng/mL occurred at 6.3 hours following multiple dosing. Peak plasma levels obtained with an immediate-release syrup occurred at approximately 1.5 hours for hydrocodone and 2.8 hours for chlorpheniramine. The plasma half-lives of hydrocodone and chlorpheniramine have been reported to be approximately 16 hours, respectively.

INDICATIONS AND USAGE

TUSSIONEX Pennkinetic Extended-Release Suspension is indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold.

CONTRAINDICATIONS

Known allergy or sensitivity to hydrocodone or chlorpheniramine.

WARNINGS

Respiratory Depression: As with all narcotics, TUSSIONEX Pennkinetic Extended-Release Suspension produces dose-related respiratory depression by directly acting on brain stem respiratory centers. Hydrocodone affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. Caution should be exercised when TUSSIONEX Pennkinetic Extended-Release Suspension is used postoperatively and in patients with pulmonary disease or whenever ventilatory function is depressed. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated (see OVERDOSAGE).

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Obstructive Bowel Disease: Chronic use of narcotics may result in obstructive bowel disease especially in patients with underlying intestinal motility disorder.

Pediatric Use: In pediatric patients, as well as adults, the respiratory center is sensitive to the depressant action of narcotic cough suppressants in a dose-dependent manner. Benefit to risk ratio should be carefully considered especially in pediatric patients with respiratory embarrassment (e.g., croup) (see PRECAUTIONS).

PRECAUTIONS

General

Caution is advised when prescribing this drug to patients with narrow-angle glaucoma, asthma or prostatic hypertrophy.

Special Risk Patients: As with any narcotic agent, TUSSIONEX Pennkinetic Extended-Release Suspension should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression kept in mind.

Information for Patients: As with all narcotics, TUSSIONEX Pennkinetic Extended-Release Suspension may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly. TUSSIONEX Pennkinetic Extended-Release Suspension must not be diluted with fluids or mixed with other drugs as this may alter the resin-binding and change the absorption rate, possibly increasing the toxicity.

Keep out of the reach of children.

Cough Reflex: Hydrocodone suppresses the cough reflex as with all narcotics, caution should be exercised when TUSSIONEX Pennkinetic Extended-Release Suspension is used postoperatively, and in patients with pulmonary disease.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents or other CNS depressants (including alcohol) concomitantly with TUSSIONEX Pennkinetic Extended-Release Suspension may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of the antidepressant or hydrocodone.

The concurrent use of other anticholinergics with hydrocodone may produce paralytic ileus.

Concomitant Therapy
In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

OVERDOSAGE

Significant lethality was observed in mice after a single oral dose of 9 g/m^2. No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m^2, respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

Few cases of overdosage with ZOCOR have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 80 mg. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended. The dialyzability of simvastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ZOCOR and should continue on this diet during treatment with ZOCOR (see NCEP Treatment Guidelines for details on dietary therapy).

The recommended starting dose is 5–10 mg once a day in the evening. The recommended dosing range is 5–40 mg/day as a single dose in the evening; the maximum recommended dose is 40 mg/day. Doses should be individualized according to baseline LDL-C levels, the recommended goal of therapy (see NCEP Guidelines) and the patient's response. Patients requiring reductions in LDL cholesterol of 20% or more to achieve their goal (see INDICATIONS AND USAGE) should be started on 10 mg/day of ZOCOR. A starting dose of 5 mg should be considered for patients requiring smaller reductions and for the elderly. Adjustments of dosage should be made at intervals of 4 weeks or more.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of ZOCOR if cholesterol falls significantly below the targeted range.

In the Scandinavian Simvastatin Survival Study (4S) [see CLINICAL PHARMACOLOGY, *Clinical Studies*], patients with coronary heart disease and hypercholesterolemia were treated with a starting dose of 20 mg of ZOCOR given as a single dose in the evening.

General Recommendations
In the elderly, maximum reductions in LDL cholesterol may be achieved with daily doses of 20 mg of ZOCOR or less.

In patients taking immunosuppressive drugs concomitantly with simvastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 5 mg of ZOCOR and should not exceed 10 mg/day.

Concomitant Therapy
ZOCOR is effective alone or when used concomitantly with bile-acid sequestrants. Use of ZOCOR with fibrate-type drugs such as gemfibrozil or clofibrate should generally be avoided (see WARNINGS; *Skeletal Muscle*).

Dosage in Patients with Renal Insufficiency
Because ZOCOR does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However, caution should be exercised when ZOCOR is administered to patients with severe renal insufficiency; such patients should be started at 5 mg/day and be closely monitored (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Skeletal Muscle*).

HOW SUPPLIED

No. 3588—Tablets ZOCOR 5 mg are buff, shield-shaped, film-coated tablets, coded MSD 726 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0726-61 unit of use bottles of 60
(6505-01-354-4549, 5 mg 60's)
NDC 0006-0726-54 unit of use bottles of 90
(6505-01-354-4548, 5 mg 90's)
NDC 0006-0726-28 unit dose packages of 100.
Shown in Product Identification Guide, page 325

No. 3589—Tablets ZOCOR 10 mg are peach, shield-shaped, film-coated tablets, coded MSD 735 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0735-61 unit of use bottles of 60
(6505-01-354-4545, 10 mg 60's)
NDC 0006-0735-54 unit of use bottles of 90
(6505-01-354-4544 10 mg 90's)
NDC 0006-0735-28 unit dose packages of 100
(6505-01-354-4543, 10 mg individually sealed 100's)
NDC 0006-0735-82 bottles of 1000
(6505-01-373-7290, 10 mg 1000's)
NDC 0006-0735-87 bottles of 10,000
(6505-01-378-8058, 10 mg 10,000's).
Shown in Product Identification Guide, page 325

No. 3590—Tablets ZOCOR 20 mg are tan, shield-shaped, film-coated tablets, coded MSD 740 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0740-61 unit of use bottles of 60
(6505-01-354-4547, 20 mg 60's)
NDC 0006-0740-82 bottles of 1000
NDC 0006-0740-87 bottles of 10,000
(6505-01-378-8771, 20 mg 10,000's).
Shown in Product Identification Guide, page 325

No. 3591—Tablets ZOCOR 40 mg are brick-red, shield-shaped, film-coated tablets, coded MSD 749 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0749-61 unit of use bottles of 60
(6505-01-354-4546, 40 mg 60's).
Shown in Product Identification Guide, page 325

Storage
Store between 5–30°C (41–86°F).

7825419 Issued November 1995

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8819 N. PIONEER ROAD
PEORIA, IL 61615

Direct Inquiries to:
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FAX: (309) 693-2158

FLORICAL® OTC
[flor ĭ cal]
(fluoride and calcium supplement)

ACTIVE INGREDIENTS
Florical® contains 3.75 mg fluoride (as sodium fluoride), 145 mg calcium (as calcium carbonate)

DIRECTIONS
Take one tablet or capsule daily, or as recommended by physician.

HOW SUPPLIED
Florical® is supplied as tablets or capsules in bottles of 100 or 500.
NDC 00394-0102 (100) and NDC 00394-0100-05

MONOCAL® OTC
[mon ō cal]
(fluoride and calcium supplement)

ACTIVE INGREDIENTS
Monocal® contains 3 mg fluoride (as monofluorophosphate) and 250 mg calcium (as calcium carbonate)

DIRECTIONS
Take one tablet daily, or as recommended by physician.

HOW SUPPLIED
Monocal® is supplied as tablets in bottles of 100.
NDC 00394-0105-02

EDUCATIONAL MATERIAL

1. SAMPLES
2. "A RANDOMIZED, CONTROLLED STUDY OF THE CHANGES IN BONE DENSITY IN RESPONSE TO MONOFLUOROPHOSPHATE AND CALCIUM IN OSTEOPOROTIC PATIENTS"
AMY E. SHAW M.D., PEGGY J. JENNINGS Ph.D, JENIFER JOWSEY Ph.D, ROBERT B. MIMS M.D. JAMES K. GUDE M.D.

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FAX: (910) 856-0107
(formerly Mayrand Pharmaceuticals)

ANATUSS® DM SYRUP OTC

DESCRIPTION
Each 5 ml of ANATUSS DM SYRUP for oral administration contains:

Guaifenesin	100 mg
Pseudoephedrine Hydrochloride	30 mg
Dextromethorphan Hydrobromide	10 mg

In a good tasting cherry flavored vehicle.

HOW SUPPLIED
ANATUSS DM SYRUP is supplied in pints NDC #0259-0383-16, 4 oz bottles NDC #0259-0383-04.

ANATUSS® DM TABLETS OTC

DESCRIPTION
Each orange, oval European scored ANATUSS DM TABLET for oral administration contains:

Guaifenesin	400 mg
Pseudoephedrine Hydrochloride	60 mg
Dextromethorphan Hydrobromide	20 mg

HOW SUPPLIED
ANATUSS DM TABLETS are available as orange, oval shaped caplets, deep-scored on one side with an "M" appearing on the left of the score and an "P" appearing on the right of the score and 0382 appearing on the bottom side of the tablet.
In bottles of 100: NDC #0259-0382-01, in bottles of 20: NDC #0259-0382-21.

ANATUSS® LA TABLETS ℞

DESCRIPTION
Each off-white European scored Anatuss LA Tablet for oral administration contains:

Guaifenesin	400 mg
Pseudoephedrine Hydrochloride	120 mg

Guaifenesin, 3-(2-methoxyphenoxy)-1,2-Propanediol, a white odorless, crystalline material with a slightly bitter aromatic taste. Pseudoephedrine Hydrochloride, [1-(methylamino) ethyl]benzenemethanol, a white crystalline, almost odorless powder with a bitter taste.

HOW SUPPLIED
Anatuss LA Tablets are available as off-white oval-shaped tablets, deep-scored on one side with an "M" appearing on the left of the score and an "R" appearing on the right of the score and 0379 appearing on the bottom side of the tablet.
In bottles of 100: NDC #0259-0379-01.

ELDERCAPS® ℞

DESCRIPTION
Each capsule contains: Vitamin A Acetate, 4000 I.U.; Vitamin D_2, 400 I.U.; Vitamin E, 25 I.U.; Ascorbic Acid, 200 mg.; Thiamine Mononitrate, 10 mg.; Riboflavin, 5 mg.; Pyridoxine HCl, 2 mg.; Niacinamide, 25 mg.; d-Calcium Pantothenate, 10 mg.; Zinc Sulfate, 110 mg.; Magnesium Sulfate, 70 mg.; Manganese Sulfate, 5 mg.; Folic Acid, 1 mg.

HOW SUPPLIED
ELDERCAPS are supplied in bottles of 100: NDC #0259-1337-01.

Continued on next page

Monarch —Cont.

WARNINGS

Hydrocodone should be prescribed and administered with the same degree of caution as all oral medications containing a narcotic analgesic. Extreme caution should be exercised in the use of hydrocodone in patients with severe respiratory impairment or patients with impaired respiratory drive.

If sympathomimetic amines are used in patients with hypertension, diabetes mellitus, ischemic heart disease, hyperthyroidism, increased intraocular pressure or prostatic hypertrophy, judicious caution should be exercised (see CONTRAINDICATIONS).

Use in Elderly: The elderly (60 years and older) are more likely to have adverse reactions to sympathomimetics. Overdosage of sympathomimetics in this age group may cause hallucinations, convulsions, CNS depression and death.

PRECAUTIONS

General: Caution should be exercised if used in patients with diabetes, hypertension, cardiovascular diseases, hyperreactivity to ephedrine, or decreased respiratory drive (see CONTRAINDICATIONS).

Information for Patients: Hydrocodone may produce drowsiness. Persons who perform hazardous tasks requiring mental alertness or physical coordination should be cautioned accordingly. Concomitant use of hydrocodone with tranquilizers, alcohol or other depressants may produce additive depressant effects. Do not exceed the prescribed dosage.

Drug Interactions: Hydrocodone may potentiate the effects of other narcotics, general anesthetics, tranquilizers, sedatives and hypnotics, tricyclic antidepressants, MAO inhibitors, alcohol, and other CNS depressants. Beta-adrenergic blockers and MAO inhibitors potentiate the sympathomimetic effects of pseudoephedrine. Sympathomimetics may reduce the antihypertensive effects of methyldopa, mecamylamine, reserpine and veratrum alkaloids.

Laboratory Test Interactions: Guaifenesin interferes with the colorimetric determination of 5-hydroxyindoleacetic acid (5-HIAA) and Vanillylmandelic acid (VMA).

Pregnancy Category C: Animal reproduction studies have not been conducted with pseudoephedrine, guaifenesin, or hydrocodone. It is also not known whether pseudoephedrine, guaifenesin or hydrocodone, can cause fetal harm when administered to a pregnant women or can affect reproduction capacity. Pseudoephedrine, guaifenesin or hydrocodone may be given to a pregnant woman only if clearly needed.

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from sympathomimetic amines, pseudoephedrine is contraindicated in nursing mothers.

ADVERSE REACTIONS

Gastrointestinal upset, nausea, drowsiness and constipation. A slight elevation in serum transaminase levels has been noted.

Individuals hyperreactive to pseudoephedrine may display ephedrine-like reactions such as tachycardia, palpitations, headache, dizziness or nausea. Sympathomimetic drugs have been associated with certain untoward reactions including fear, anxiety, tenseness, restlessness, tremor, weakness, pallor, respiratory difficulty, dysuria, insomnia, hallucinations, convulsions, CNS depression, arrhythmias, and cardiovascular collapse with hypotension. Patient idiosyncrasy to adrenergic agents may be manifested by insomnia, dizziness, weakness, tremor or arrhythmias.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone in TUSSEND® EXPECTORANT is controlled by the Drug Enforcement Administration. TUSSEND® EXPECTORANT is a Schedule III controlled substance.

Abuse: Hydrocodone is a narcotic drug related to codeine with similar abuse potential.

Dependence: Hydrocodone can produce drug dependence of the morphine type. Psychic dependence, physical dependence and tolerance may develop if dosage recommendations are greatly exceeded over a prolonged period of time.

OVERDOSAGE

Acute overdosage with TUSSEND® EXPECTORANT may produce variable clinical signs as hydrocodone produces CNS depression and cardiovascular depression while pseudoephedrine produces CNS stimulation and variable cardiovascular effects Hydrocodone is likely to be responsible for most of the severe reactions from overdosage. Pressor amines should be used with great caution when taking pseudoephedrine. Patients with signs of stimulation should be treated conservatively and depressant medications should be avoided if possible because of potential drug interaction with hydrocodone.

DOSAGE AND ADMINISTRATION

ADULTS: Two teaspoonfuls (10 mL) every 4–6 hours. **CHILDREN 6–12 Years:**

One teaspoonful (5 mL) every 4–6 hours. May be given four times a day as needed. May be taken with meals.

CAUTION:

Federal (USA) law prohibits dispensing without prescription.

HOW SUPPLIED

TUSSEND® EXPECTORANT is a red-colored, fruit punch-flavored liquid supplied in bottles of one pint (16 fl. oz.), NDC 61570-005-16.

Storage: Store at controlled room temperature, 15°–30°C (59°–86°F). Dispense in a tight, light-resistant container as described in USP

Manufactured for: Monarch Pharmaceuticals, Bristol, TN 37620

Revised 6/95
0932361

Shown in Product Identification Guide, page 325

Muro Pharmaceutical, Inc.

890 EAST STREET
TEWKSBURY, MA 01876-1496

Direct Inquiries to:
Professional Service Department
(800) 225-0974
(508) 851-5981

BROMFED® CAPSULES Rx

[*brōm 'fĕd*]

A light green and clear capsule containing white beads. Extended-Release.

Each capsule contains:

Brompheniramine maleate	12 mg
Pseudoephedrine hydrochloride	120 mg

in a specially prepared base to provide prolonged action.

BROMFED-PD® CAPSULES Rx

A dark green and clear capsule containing white beads. Extended-Release.

Each capsule contains:

Brompheniramine maleate	6 mg
Pseudoephedrine hydrochloride	60 mg

in a specially prepared base to provide prolonged action.

BROMFED® and BROMFED-PD® CAPSULES also contain inactive ingredients: benzyl alcohol, butyl paraben, carboxymethylcellulose sodium, D & C yellow #10, edetate calcium disodium, FD&C blue #1, FD&C yellow #6, gelatin, methyl paraben, pharmaceutical glaze, propyl paraben, sodium lauryl sulfate, sodium propionate, starch, sucrose and other ingredients.

BROMFED® TABLETS Rx

A white scored tablet.

Each tablet contains:

Brompheniramine maleate	4 mg
Pseudoephedrine hydrochloride	60 mg

Also contains as inactive ingredients colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

BROMFED® contains ingredients of the following therapeutic classes: antihistamine and nasal decongestant.

CLINICAL PHARMACOLOGY

Brompheniramine maleate is an alkylamine type antihistamine. This group of antihistamines are among the most active histamine antagonists and are generally effective in relatively low doses. The drugs are not so prone to produce drowsiness and are among the most suitable agents for day time use; but again, a significant proportion of patients do experience this effect. Pseudoephedrine hydrochloride is a sympathomimetic which acts predominently on alpha receptors and has little action on beta receptors. It therefore functions as an oral nasal decongestant with minimal CNS stimulation.

INDICATIONS

For the temporary relief of symptoms of seasonal and perennial allergic rhinitis, and vasomotor rhinitis, including nasal obstruction (congestion).

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients. Also contraindicated in patients with severe hypertension, severe coronary artery disease, patients on MAO inhibitor therapy, patients with narrow-angle glaucoma, urinary retention, peptic ulcer and during an asthmatic attack.

WARNINGS

Considerable caution should be exercised in patients with hypertension, diabetes mellitus, ischemic heart disease, hyperthyroidism, increased intraocular pressure and prostatic hypertrophy. The elderly (60 years or older) are more likely to exhibit adverse reactions.

Antihistamines may cause excitability, especially in children. At dosages higher than the recommended dose, nervousness, dizziness or sleeplessness may occur.

PRECAUTIONS

General: Caution should be exercised in patients with high blood pressure, heart disease, diabetes or thyroid disease. The antihistamine in this product may exhibit additive effects with other CNS depressants, including alcohol.

Information for Patients: Antihistamine may cause drowsiness and ambulatory patients who operate machinery or motor vehicles should be cautioned accordingly.

Drug Interactions: MAO inhibitors and beta adrenergic blockers increase the effects of sympathomimetics. Sympathomimetics may reduce the antihypertensive effects of methyldopa, mecamylamine, reserpine and veratrum alkaloids. Concomitant use of antihistamines with alcohol and other CNS depressants may have an additive effect.

Pregnancy: The safety of use of this product in pregnancy has not been established.

ADVERSE REACTIONS

Adverse reactions include drowsiness, lassitude, nausea, giddiness, dryness of mouth, blurred vision, cardiac palpitations, flushing, increased irritability or excitement (especially in children).

DOSAGE AND ADMINISTRATION

BROMFED® CAPSULES Adults and children 12 years of age and over: 1 capsule every 12 hours.

BROMFED-PD® CAPSULES Adults and children 12 years of age and over: 1 or 2 capsules every 12 hours. Children 6 to under 12 years of age: 1 capsule every 12 hours.

BROMFED® TABLETS Adults and children 12 years of age and over: One tablet every 4 hours not to exceed 6 doses in 24 hours. Children 6 to under 12 years of age: One-half tablet every 4 hours not to exceed 6 doses in 24 hours. Do not give to children under 6 years except under the advice and supervision of a physician.

HOW SUPPLIED

BROMFED® CAPSULES. Bottle of 100 (NDC 0451-4000-50) and 500 (NDC 0451-4000-60). Each capsule is coded "BROMFED" "MURO 12-120".

BROMFED-PD® CAPSULES. Bottle of 100 (NDC 0451-4001-50) and 500 (NDC 0451-4001-60). Each capsule is coded "BROMFED-PD" "MURO 6-60".

BROMFED® TABLETS. Bottle of 100 (NDC 0451-4060-50). Each tablet is coded "MURO 4060" on one side and scored on the reverse side.

Dispense in tight child-resistant containers as defined in USP/NF. Store at controlled room temperature.

BROMFED® SYRUP OTC

[*brōm 'fĕd*]

(See PDR For Nonprescription Drugs.)

BROMFED-DM® COUGH SYRUP Rx

[*brōm 'fĕd*]

DESCRIPTION

BROMFED-DM® Cough Syrup is a cherry flavored red syrup.

Each 5 mL (1 teaspoonful) contains:

Brompheniramine Maleate, USP	2 mg
Pseudoephedrine Hydrochloride, USP	30 mg
Dextromethorphan Hydrobromide, USP	10 mg

Inactive Ingredients: Citric Acid, FD&C Red 40, FD&C Blue #1, Wild Cherry Flavor, Glycerin, Saccharin Sodium, Sodium Benzoate, Sorbitol, Sucrose, Methylparaben, Purified Water.

Antihistamine/Nasal Decongestant/Antitussive syrup for oral administration.

CLINICAL PHARMACOLOGY

Brompheniramine maleate is a histamine antagonist, specifically an H_1-receptor-blocking agent belonging to the alkylamine class of antihistamines. Antihistamines appear to compete with histamine for receptor sites on effector cells. Brompheniramine also has anticholinergic (drying) and sedative effects. Among the antihistaminic effects, it antagonizes the allergic response (vasodilatation, increased vascular permeability, increased mucus secretion) of nasal tissues. Brompheniramine is well absorbed from the gastrointestinal tract, with peak plasma concentration after single, oral dose of 4 mg reached in 5 hours; urinary excretion is the major route of elimination, mostly as products of biodegradation; the liver is assumed to be the main site of metabolic transformation.

Pseudoephedrine acts on sympathetic nerve endings and also on smooth muscle, making it useful as a nasal decongestant. The nasal decongestant effect is mediated by the action of pseudoephedrine on α-sympathetic receptors, produc-

vasoconstriction of the dilated nasal arterioles. Following oral administration, effects are noted within 30 minutes with peak activity occurring at approximately one hour. Dextromethorphan acts centrally to elevate the threshold for coughing. It has no analgesic or addictive properties. The onset of antitussive action occurs in 15 to 30 minutes after administration and is of long duration.

INDICATIONS AND USAGE

For relief of coughs and upper respiratory symptoms, including nasal congestion, associated with allergy or the common cold.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients. Do not use in the newborn, in premature infants, in nursing mothers, in patients with severe hypertension or severe coronary artery disease, or in those receiving monoamine oxidase (MAO) inhibitors.

Antihistamines should not be used to treat lower respiratory tract conditions including asthma.

WARNINGS

Especially in infants and small children, antihistamines in overdosage may cause hallucinations, convulsions, and death.

Antihistamines may diminish mental alertness. In the young child, they may produce excitation.

PRECAUTIONS

General: Because of its antihistamine component, **BROMFED-DM® Cough Syrup** should be used with caution in patients with a history of bronchial asthma, narrow angle glaucoma, gastrointestinal obstruction, or urinary bladder neck obstruction. Because of its sympathomimetic component, **BROMFED-DM® Cough Syrup** should be used with caution in patients with diabetes, hypertension, heart disease, or thyroid disease.

Information for Patients: Patients should be warned about engaging in activities requiring mental alertness, such as driving a car or operating dangerous machinery.

Drug Interactions: Antihistamines have additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, antianxiety agents, etc.) MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines. MAO inhibitors may enhance the effect of pseudoephedrine. Sympathomimetics may reduce the effects of antihypertensive drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal studies of **BROMFED-DM® Cough Syrup** to assess the carcinogenic and mutagenic potential of the effect on fertility have not been performed.

Pregnancy

Teratogenic Effects—Pregnancy Category C

Animal reproduction studies have not been conducted with **BROMFED-DM® Cough Syrup.** It is also not known whether **BROMFED-DM® Cough Syrup** can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. **BROMFED-DM® Cough Syrup** should be given to a pregnant woman only if clearly needed.

Reproduction studies of brompheniramine maleate (a component of **BROMFED-DM® Cough Syrup**) in rats and mice at doses up to 16 times the maximum human dose have revealed no evidence of impaired fertility or harm to the fetus.

Nursing Mothers: Because of the higher risk of intolerance of anithistamines in small infants generally, and in newborns and prematures in particular, **BROMFED-DM® Cough Syrup** is contraindicated in nursing mothers.

ADVERSE REACTIONS

The most frequent adverse reaction to **BROMFED-DM® Cough Syrup** are: sedation, dryness of mouth, nose and throat; thickening of bronchial secretions; dizziness. Other adverse reactions may include:

Dermatologic: Urticaria, drug rash, photosensitivity, pruritus.

Cardiovascular System: Hypotension, hypertension, cardiac arrhythmias, palpitation.

CNS: Disturbed coordination, tremor, irritability, insomnia, visual disturbances, weakness, nervousness, convulsions, headache, euphoria, and dysphoria.

G.U. System: Urinary frequency, difficult urination.

G.I. System: Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Tightness of chest and wheezing, shortness of breath.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

OVERDOSAGE

Signs and Symptoms: Central nervous system effects from overdosage of brompheniramine may vary from depression to stimulation, especially in children. Anticholinergic effects may be noted. Toxic doses of pseudoephedrine may result in CNS stimulation, tachycardia, hypertension, and cardiac arrhythmias; signs of CNS depression may occasionally be seen. Dextromethorphan in toxic doses will cause drowsiness, ataxia, nystagmus, opisthotonos, and convulsive seizures.

Toxic Doses: Data suggest that individuals may respond in an unexpected manner to apparently small amounts of a particular drug. A 2½-year old child survived the ingestion of 21 mg/kg of dextromethorphan exhibiting only ataxia, drowsiness, and fever, but seizures have been reported in 2 children following the ingestion of 13–17 mg/kg. Another 2½-year old child survived a dose of 300–900 mg of brompheniramine. The toxic dose of pseudoephedrine should be less than that of ephedrine, which is estimated to be 50 mg/kg.

Treatment: Induce emesis if patient is alert and is seen prior to 6 hours following ingestion. Precautions against aspiration must be taken, especially in infants and small children. Gastric lavage may be carried out, although in some instances tracheostomy may be necessary prior to lavage. Naloxone hydrochloride 0.005 mg/kg intravenously may be of value in reversing the CNS depression that may occur from an overdose of dextromethorphan. CNS stimulants may counter CNS depression. Should CNS hyperactivity or convulsive seizures occur, intravenous short-acting barbiturates may be indicated. Hypertensive responses and/or tachycardia should be treated appropriately. Oxygen, intravenous fluids, and other supportive measures should be employed as indicated.

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age and over: 2 teaspoonfuls every 4 hours. Children 6 to under 12 years: 1 teaspoonful every 4 hours. Children 2 to under 6 years: ½ teaspoonful every 4 hours. Children 6 months to under 2 years: Dosage to be established by physician.

Do not exceed 6 doses during a 24-hour period.

HOW SUPPLIED

BROMFED-DM® Cough Syrup is a red syrup containing in each 5 mL (1 teaspoonful) brompheniramine maleate 2 mg, pseudoephedrine hydrochloride 30 mg and dextromethorphan hydrobromide 10 mg, available in Bottles of 16 fl. oz. (NDC #0451-4101-16.)

Store at controlled room temperature, between 15°C and 30°C (59°F and 86°F).

Dispense in tight, light-resistant, and child-resistant containers as defined in U.S.P./NF.

GUAIFED® CAPSULES

℞

[gwī'ah-fed]

A white opaque and clear capsule containing white beads.

Extended-Release

Each capsule contains:

Pseudoephedrine hydrochloride	120 mg

in a specially prepared base to provide prolonged action.

Guaifenesin	250 mg

designed for immediate release to provide rapid action.

GUAIFED–PD® CAPSULE

℞

A blue and clear capsule containing white beads.

Extended-Release

Each capsule contains:

Pseudoephedrine hydrochloride	60 mg

in a specially prepared base to provide prolonged action.

Guaifenesin	300 mg

designed for immediate release to provide rapid action.

GUAIFED® and GUAIFED–PD® CAPSULES also contain as inactive ingredients: Benzyl Alcohol, Butyl Paraben, Edetate Calcium Disodium, Gelatin, Methyl Paraben, Pharmaceutical Glaze, Propyl Paraben, Sodium Lauryl Sulfate, Sodium Propionate, Starch, Sucrose, Titanium Dioxide, FD&C Blue #1 (GUAIFED-PD® only) and other ingredients.

GUAIFED® and GUAIFED–PD® contains ingredients of the following therapeutic classes: nasal decongestant and expectorant.

CLINICAL PHARMACOLOGY

Pseudoephedrine hydrochloride is a sympathomimetic which acts predominantly on alpha adrenergic receptors in the mucosa of the respiratory tract, producing vasoconstriction and has little action on beta receptors. It therefore functions as an oral nasal decongestant with minimal CNS stimulation. Pseudoephedrine hydrochloride also increases sinus drainage and secretions. Guaifenesin is an expectorant which increases the output of phlegm (sputum) and bronchial secretions by reducing adhesiveness and surface tension. The increased flow of less viscid secretions promotes ciliary action and changes a dry, unproductive cough to one that is more productive and less frequent.

INDICATIONS

For temporary relief of nasal congestion and dry non-productive cough associated with the common cold and other respiratory allergies. Helps drainage of the bronchial tubes by thinning the mucus.

CONTRAINDICATIONS

This product is contraindicated in patients with a known hypersensitivity to any of its ingredients. Also contraindicated in patients with severe hypertension, severe coronary artery disease and patients on MAO inhibitor therapy. Should not be used during pregnancy or in nursing mothers. Considerable caution should be exercised in patients with hypertension, diabetes mellitus, ischemic heart disease, hyperthyroidism, increased intraocular pressure and prostatic hypertrophy. The elderly (60 years or older) are more likely to exhibit adverse reactions. At dosages higher than the recommended dose, nervousness, dizziness or sleeplessness may occur.

WARNINGS

Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician. This medication should be taken a few hours prior to bedtime to minimize the possibility of sleeplessness. Take this medication with a glass of water after each dose, to help loosen mucus in the lungs.

PRECAUTIONS

General: Caution should be exercised in patients with high blood pressure, heart disease, diabetes or thyroid disease and in patients who exhibit difficulty in urination due to enlargement of the prostate gland. Check with a physician if symptoms do not improve within 7 days or if accompanied by high fever, rash or persistent headache.

Drug Interactions: Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting a physician. MAO inhibitors and beta adrenergic blockers may increase the effect of sympathomimetics. Sympathomimetics may reduce the antihypertensive effects of methyldopa, mecamylamine, reserpine and veratrum alkaloids. Pseudoephedrine hydrochloride may increase the possibility of cardiac arrhythmias in patients presently taking digitalis glycosides.

Pregnancy: Pregnancy Catagory B. It has been shown that pseudoephedrine hydrochloride can cause reduced average weight, length, and rate of skeletal ossification in the animal fetus.

Nursing Mothers: Pseudoephedrine is excreted in breast milk; use by nursing mother is not recommended because of the higher than usual risk of side effects from sympathomimetic amines for infants, especially newborn and premature infants.

Geriatrics: Pseudoephedrine should be used with caution in the elderly because they may be more sensitive to the effects of the sympathomimetics.

ADVERSE REACTIONS

Adverse reactions include nausea, cardiac palpitations, increased irritability or excitement, headache, dizziness, tachycardia, diarrhea, drowsiness, stomach pain, seizures, slowed heart rate, shortness of breath and/or troubled breathing.

OVERDOSAGE

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN. IN CASE OF SUSPECTED OVERDOSE, IMMEDIATELY CALL YOUR REGIONAL POISON CONTROL CENTER and/or SEEK PROFESSIONAL ASSISTANCE.

Symptoms of overdosage may be caused by pseudoephedrine. Symptoms of overdosage with pseudoephedrine include anxiety, tenseness, respiratory difficulty, headache and awareness of the slow forceful heartbeat.

TREATMENT OF OVERDOSE

The stomach should be emptied promptly by emetics and/or gastric lavage. The installation of activated charcoal also should be considered. Cardiac function and serum electrolytes should be monitored and treatment instigated if indicated. If convulsions or marked CNS excitement occurs, diazepam may be used.

DOSAGE AND ADMINISTRATION

GUAIFED® CAPSULES Adults and children 12 years of age and over: 1 capsule every 12 hours.

GUAIFED–PD® CAPSULES Adults and children 12 years of age and over: 1 or 2 capsules every 12 hours. Children 6 to under 12 years of age: 1 capsule every 12 hours.

HOW SUPPLIED

GUAIFED® CAPSULES Bottle of 100 (NDC 0451-4002-50). Bottle of 500 (NDC 0451-4002-60). Each capsule is coded "GUAIFED" "MURO 120-250".

GUAIFED–PD® CAPSULES Bottle of 100 (NDC 0451-4003-50). Bottle of 500 (NDC 0451-4003-60). Each capsule is coded "GUAIFED-PD" "MURO 60-300".

Dispense in tight, child-resistant containers as defined in USP/NF. Store at controlled room temperature, between 15°–30°C (59°–86°F).

Keep this and all drugs out of reach of children.

Continued on next page

Organon—Cont.

COMPATIBILITY
Norcuron® is compatible in solution with:
0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers
Use within 24 hours of mixing with the above solutions.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED
10 mL vials (10 mg of vecuronium bromide) and 10 mL prefilled syringes of diluent (bacteriostatic water for injection, USP) 22g 1¼" needle.
Boxes of 10 NDC No. 0052-0441-60
10 mL vials (10 mg vecuronium bromide) and 10 mL vials of diluent (bacteriostatic water for injection, USP).
Boxes of 10 NDC No. 0052-0441-17
10 mL vials (10 mg vecuronium bromide) only; DILUENT NOT SUPPLIED.
Boxes of 10 NDC No. 0052-0441-15
20 mL vials (20 mg vecuronium bromide) only; DILUENT NOT SUPPLIED.
Boxes of 10 NDC No. 0052-0442-46

STORAGE
15–30°C (59–86°F). Protect from light.

AFTER RECONSTITUTION
- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

Caution: Federal law prohibits dispensing without prescription.

ORGANON INC.
WEST ORANGE, NEW JERSEY 07052
5310125 REVISED 7/93

PAVULON®
[*pāv-u-lon*]
(pancuronium bromide) injection

HOW SUPPLIED
2 mL ampuls—2 mg/mL—boxes of 25—NDC-0052-0444-26
5 mL ampuls—2 mg/mL—boxes of 25—NDC-0052-0444-25
10 mL vials—1 mg/mL—boxes of 25—NDC-0052-0443-25

PREGNYL®
(chorionic gonadotropin for injection, U.S.P.)

DESCRIPTION
Human chorionic gonadotropin (HCG), a polypeptide hormone produced by the human placenta, is composed of an alpha and a beta sub-unit. The alpha sub-unit is essentially identical to the alpha sub-units of the human pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), as well as to the alpha sub-unit of human thyroid-stimulating hormone (TSH). The beta sub-units of these hormones differ in amino acid sequence.
PREGNYL® (chorionic gonadotropin for injection, USP) is a highly purified pyrogen-free preparation obtained from the urine of pregnant females. It is standardized by a biological assay procedure. It is available for intramuscular injection in multiple dose vials containing 10,000 USP Units of sterile dried powder with 5 mg. monobasic sodium phosphate and 4.4 mg. dibasic sodium phosphate. If required, pH is adjusted with sodium hydroxide and/or phosphoric acid. Each package also contains a 10 mL vial of solvent (water for injection with 0.56% sodium chloride and 0.9% benzyl alcohol). If required, pH is adjusted with sodium hydroxide and/or hydrochloric acid.

CLINICAL PHARMACOLOGY
The action of HCG is virtually identical to that of pituitary LH although HCG appears to have a small degree of FSH activity as well. It stimulates production of gonadal steroid hormones by stimulating the interstitial cells, (Leydig cells) of the testis to produce androgens and the corpus luteum of the ovary to produce progesterone.
Androgen stimulation in the male leads to the development of secondary sex characteristics and may stimulate testicular descent when no anatomical impediment to descent is present. This descent is usually reversible when HCG is discontinued. During the normal menstrual cycle, LH participates with FSH in the development and maturation of the normal ovarian follicle and the mid-cycle LH surge triggers ovulation. HCG can substitute for LH in this function.
During a normal pregnancy, HCG secreted by the placenta maintains the corpus luteum after LH secretion decreases, supporting continued secretion of estrogen and progesterone and preventing menstruation. HCG HAS NO KNOWN EFFECT ON FAT MOBILIZATION, APPETITE OR SENSE OF HUNGER, OR BODY FAT DISTRIBUTION.

INDICATIONS
HCG HAS NOT BEEN DEMONSTRATED TO BE EFFECTIVE ADJUNCTIVE THERAPY IN THE TREATMENT OF OBESITY. THERE IS NO SUBSTANTIAL EVIDENCE THAT IT INCREASES WEIGHT LOSS BEYOND THAT RESULTING FROM CALORIC RESTRICTION, THAT IT CAUSES A MORE ATTRACTIVE OR "NORMAL" DISTRIBUTION OF FAT, OR THAT IT DECREASES THE HUNGER AND DISCOMFORT ASSOCIATED WITH CALORIE-RESTRICTED DIETS.
1. Prepubertal cryptorchidism not due to anatomical obstruction. In general, HCG is thought to induce testicular descent in situations when descent would have occurred at puberty. HCG thus may help predict whether or not orchiopexy will be needed in the future. Although, in some cases, descent following HCG administration is permanent, in most cases, the response is temporary. Therapy is usually instituted between the ages 4 and 9.
2. Selected cases of hypogonadotropic hypogonadism (hypogonadism secondary to a pituitary deficiency) in males.
3. Induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure and who has been appropriately pretreated with human menotropins.

CONTRAINDICATIONS
Precocious puberty, prostatic carcinoma or other androgen-dependent neoplasm, prior allergic reaction to HCG.

WARNINGS
HCG should be used in conjunction with human menopausal gonadotropins only by physicians experienced with infertility problems who are familiar with the criteria for patient selection, contraindications, warnings, precautions and adverse reactions described in the package insert for menotropins.
The principal serious adverse reactions during this use are: (1) Ovarian hyperstimulation, a syndrome of sudden ovarian enlargement, ascites with or without pain, and/or pleural effusion, (2) Rupture of ovarian cysts with resultant hemoperitoneum, (3) Multiple births, and (4) Arterial thromboembolism.

PRECAUTIONS
1. Induction of androgen secretion by HCG may induce precocious puberty in patients treated for cryptorchidism. Therapy should be discontinued if signs of precocious puberty occur.
2. Since androgens may cause fluid retention, HCG should be used with caution in patients with cardiac or renal disease, epilepsy, migraine, or asthma.

ADVERSE REACTIONS
Headache, irritability, restlessness, depression, fatigue, edema, precocious puberty, gynecomastia, pain at the site of injection.

DOSAGE AND ADMINISTRATION
(For Intramuscular Use Only): The dosage regimen employed in any particular case will depend upon the indication for use, the age and weight of the patient, and the physician's preference. The following regimens have been advocated by various authorities:
Prepubertal cryptorchidism not due to anatomical obstruction.
1. 4,000 U.S.P. Units three times weekly for three weeks.
2. 5,000 U.S.P. Units every second day for four injections.
3. 15 injections of 500 to 1,000 U.S.P. Units over a period of six weeks.
4. 500 U.S.P. Units three times weekly for four to six weeks. If this course of treatment is not successful, another series is begun one month later, giving 1,000 U.S.P. Units per injection.

Selected cases of hypogonadotropic hypogonadism in males.
1. 500 to 1,000 U.S.P. Units three times a week for three weeks, followed by the same dose twice a week for three weeks.
2. 4,000 U.S.P. Units three times weekly for six to nine months, following which the dosage may be reduced to 2,000 U.S.P. Units three times weekly for an additional three months.

Induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure and who has been appropriately pre-treated with human menotropins. (See prescribing information for menotropins for dosage and administration for that drug product).
5,000 to 10,000 USP Units one day following the last dose of menotropins. (A dosage of 10,000 U.S.P. Units is recommended in the labeling for menotropins).

IMPORTANT: USE COMPLETELY AFTER RECONSTITUTION. RECONSTITUTED SOLUTION IS STABLE FOR 60 DAYS WHEN REFRIGERATED.

HOW SUPPLIED
Two-vial package containing:
1–10 mL lyophilized multiple dose vial containing:
10,000 USP Units chorionic gonadotropin per vial (NDC 0052-0315-10)
1–10 mL vial of solvent containing:
water for injection with 0.56% sodium chloride and 0.9% benzyl alcohol (NDC 0052-0325-10.)

When reconstituted, each 10 mL vial contains:

Chorionic gonadotropin	10,000 USP Units
Monobasic sodium phosphate	5 mg.
Dibasic sodium phosphate	4.4 mg.
Sodium chloride	0.56%
Benzyl alcohol	0.9%

If required pH adjusted with sodium hydroxide and/or phosphoric acid.

STORAGE
Store at 15°–30°C (59°–86°F). Reconstituted material will remain stable for 60 days when refrigerated.

CAUTION
Federal law prohibits dispensing without prescription.

DIRECTIONS FOR RECONSTITUTION
Two vial package: Withdraw sterile air from lyophilized vial and inject into diluent vial. Remove 1–10 mL from diluent and add to lyophilized vial; agitate gently until powder is completely dissolved in solution.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Revised 12/90

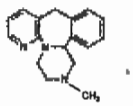
REGONOL®
[*re-gō-nol*]
(pyridostigmine bromide) injection, USP

HOW SUPPLIED
5 mg/mL: 2 mL ampuls—boxes of 25—NDC-0052-0460-02
5 mg/mL: 5 mL vials— boxes of 25—NDC-0052-0460-05

REMERON™
(mirtazapine) Tablets

5310140 4/96

DESCRIPTION
REMERON™ (mirtazapine) is an antidepressant for oral administration. It has a tetracyclic chemical structure unrelated to selective serotonin reuptake inhibitors, tricyclics or monoamine oxidase inhibitors (MAOI). Mirtazapine belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a]pyrido [2,3-c]benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:



Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.
REMERON™ is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine. Each tablet also contains corn starch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose and other inactive ingredients.

CLINICAL PHARMACOLOGY
Pharmacodynamics
The mechanism of action of REMERON™ (mirtazapine), as with other antidepressants, is unknown.
Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. These studies have shown that mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity.
Mirtazapine is a potent antagonist of 5-HT_2 and 5-HT_3 receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

Mirtazapine is a potent antagonist of histamine (H_1) receptors, a property that may explain its prominent sedative effects.

Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property that may explain the occasional orthostatic hypotension reported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the relatively low incidence of anticholinergic side effects associated with its use.

Pharmacokinetics

REMERON™ (mirtazapine) is rapidly and completely absorbed following oral administration and has a half-life of about 20–40 hours. Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment.

Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. In vitro data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas cytochrome 3A is considered to be responsible for the formation of the N-desmethyl and N-oxide metabolite. Mirtazapine has an absolute bioavailability of about 50%. It is eliminated predominantly via urine (75%) with 15% in feces. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (−) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about three times as high as that of the (+) enantiomer.

Plasma levels are linearly related to dose over a dose range of 15 to 80 mg. The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20–40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females *vs.* 26 hours for males). Steady state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio = 1.5).

Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 μg/mL.

Population Subgroups

Liver Disease—Following a single 15 mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering REMERON™ (mirtazapine) to patients with compromised hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Disease—Following a single 15 mg oral dose of mirtazapine, patients with moderate [glomerular filtration rate (GFR) = 11–39 mL/min/1.73 m^2] and severe [GFR < 10 mL/min/1.73 m^2] renal impairment had reductions in mean oral clearance of mirtazapine of about 30% and 50%, respectively, compared to normal subjects. Caution is indicated in administering REMERON™ to patients with compromised renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly Patients—Following oral administration of mirtazapine 20 mg/day for 7 days to subjects of varying ages (range, 25–74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering REMERON™ to elderly patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Clinical Trials Showing Effectiveness

The efficacy of REMERON™ (mirtazapine) as a treatment for depression was established in four placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depression. Patients were titrated with mirtazapine from a dose range of 5 mg up to 35 mg/day. Overall, these studies demonstrated mirtazapine to be superior to placebo on at least three of the following four measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery and Asberg Depression Rating Scale (MADRS). Superiority of mirtazapine over placebo was also found for certain factors of the HDRS including anxiety/somatization factor and sleep disturbance factor. The mean mirtazapine dose for patients who completed these four studies ranged from 21 to 32 mg/day. A fifth study of similar design utilized a higher dose (up to 50 mg) per day and also showed effectiveness.

Examination of age and gender subsets of the population did not reveal any differential responsiveness on the basis of these subgroupings.

INDICATIONS AND USAGE

REMERON™ (mirtazapine) Tablets are indicated for the treatment of depression.

The efficacy of REMERON™ in the treatment of depression was established in six week controlled trials of outpatients whose diagnoses corresponded most closely to the Diagnostic and Statistical Manual of Mental Disorders–3rd edition (DSM-III) category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant effectiveness of REMERON™ (mirtazapine) in hospitalized depressed patients has not been adequately studied.

The effectiveness of REMERON™ in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use REMERON™ for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

REMERON™ (mirtazapine) Tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS

Agranulocytosis

In premarketing clinical trials, two (one with Sjögren's Syndrome) out of 2,796 patients treated with REMERON™ (mirtazapine) Tablets developed agranulocytosis [absolute neutrophil count (ANC) < 500/mm^3 with associated signs and symptoms, e.g., fever, infection, etc.] and a third patient developed severe neutropenia [ANC < 500/mm^3 without any associated symptoms]. For these three patients, onset of severe neutropenia was detected on days 61, 9, and 14 of treatment, respectively. All three patients recovered after REMERON™ was stopped. These three cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per thousand patients exposed, with a very wide 95% confidence interval, i.e., 2.2 cases per 10,000 to 3.1 cases per 1000. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with REMERON™ should be discontinued and the patient should be closely monitored.

MAO Inhibitors

In patients receiving other antidepressants in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued an antidepressant drug and then are started on an MAOI, there have been reports of serious, and sometimes fatal, reactions, e.g., including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging from agitation to coma. Although there are no human data pertinent to such an interaction with REMERON™ (mirtazapine), it is recommended that REMERON™ not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

General

Somnolence

In U.S. controlled studies, somnolence was reported in 54% of patients treated with REMERON™ (mirtazapine), compared to 18% for placebo and 60% for amitriptyline. In these studies, somnolence resulted in discontinuation for 10.4% of REMERON™ treated patients, compared to 2.2% for placebo. It is unclear whether or not tolerance develops to the somnolent effects of REMERON™. Because of REMERON™'s potentially significant effects on impairment of performance, patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance (see Information for Patients).

Dizziness

In U.S. controlled studies, dizziness was reported in 7% of patients treated with REMERON™ (mirtazapine), compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of REMERON™.

Increased Appetite/Weight Gain

In U.S. controlled studies, appetite increase was reported in 17% of patients treated with REMERON™ (mirtazapine), compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of ≥ 7% of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pool of premarketing U.S. studies, including many patients in long-term, open label treatment, 8% of patients receiving REMERON™ discontinued for weight gain.

Cholesterol/Triglycerides

In U.S. controlled studies, nonfasting cholesterol increases to ≥ 20% above the upper limits of normal were observed in 15% of patients treated with REMERON™ (mirtazapine), compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases to ≥ 500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline.

Transaminase Elevations

Clinically significant ALT (SGPT) elevations (≥ 3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to REMERON™ (mirtazapine) in a pool of short-term U.S. controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3/181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued REMERON™ treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see Pharmacokinetics section of CLINICAL PHARMACOLOGY, and DOSAGE AND ADMINISTRATION).

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of REMERON™ (mirtazapine) treated patients in U.S. studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania.

Seizure

In premarketing clinical trials only one seizure was reported among the 2,796 U.S. and non-U.S. patients treated with REMERON™ (mirtazapine). However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients.

Suicide

Suicidal ideation is inherent in depression and may persist until significant remission occurs. As with any patient receiving antidepressants, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of REMERON™ (mirtazapine) should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness

Clinical experience with REMERON™ (mirtazapine) in patients with concomitant systemic illness is limited. Accordingly, care is advisable in prescribing mirtazapine for patients with diseases or conditions that affect metabolism or hemodynamic responses.

Mirtazapine has not been systematically evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or other significant heart disease. Mirtazapine was not associated with clinically significant ECG abnormalities in U.S. and non-U.S. placebo controlled trials. Mirtazapine was associated with significant orthostatic hypotension in early clinical pharmacology trials with normal volunteers. Orthostatic hypotension was infrequently observed in clinical trials with depressed patients. REMERON™ should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medication).

Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) = 11–39 mL/min/1.73 m^2] and severe [GFR < 10 mL/min/1.73 m^2] renal impairment, and also in patients with hepatic impairment (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY). Caution is indicated in administering REMERON™ to such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe REMERON™ (mirtazapine):

Agranulocytosis

Patients who are to receive REMERON™ (mirtazapine) should be warned about the risk of developing agranulocytosis. Patients should be advised to contact their physician if they experience any indication of infection such as fever, chills, sore throat, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

Interference with Cognitive and Motor Performance

REMERON™ (mirtazapine) may impair judgement, thinking, and, particularly, motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may impair a patient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should

Continued on next page

Organon—Cont.

be cautioned about engaging in hazardous activities until they are reasonably certain that REMERON™ therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with REMERON™ (mirtazapine) therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication

Patients should be advised to inform their physician if they are taking, or intend to take, any prescription or over-the-counter drugs since there is a potential for REMERON™ (mirtazapine) to interact with other drugs.

Alcohol

The impairment of cognitive and motor skills produced by REMERON™ (mirtazapine) has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during REMERON™ (mirtazapine) therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory Tests

There are no routine laboratory tests recommended.

Drug Interactions

As with other drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic inhibition or enhancement, etc.) is a possibility (see CLINICAL PHARMACOLOGY).

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of REMERON™ (mirtazapine) may be affected by the induction or inhibition of drug-metabolizing enzymes.

Drugs that are Metabolized by and/or Inhibit Cytochrome P450 Enzymes

Many drugs are metabolized by and/or inhibit various cytochrome P450 enzymes, e.g., 2D6, 1A2, 3A4, etc. In vitro studies have shown that REMERON™ (mirtazapine) is a substrate for several of these enzymes, including 2D6, 1A2, and 3A4. While in vitro studies have shown that mirtazapine is not a potent inhibitor of any of these enzymes, an indication that mirtazapine is not likely to have a clinically significant inhibitory effect on the metabolism of other drugs that are substrates for these cytochrome P450 enzymes, the concomitant use of mirtazapine with most other drugs metabolized by these enzymes has not been formally studied. Consequently, it is not possible to make any definitive statements about the risks of coadministration of mirtazapine with such drugs.

Alcohol

Concomitant administration of alcohol (equivalent to 60 g) had a minimal effect on plasma levels of REMERON™ (mirtazapine) (15 mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by REMERON™ were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking REMERON™.

Diazepam

Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by REMERON™ (mirtazapine) has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking REMERON™.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted with REMERON™ (mirtazapine) given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m^2 basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggest that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been high enough to fully characterize the carcinogenic potential of REMERON™.

Mutagenesis

REMERON™ (mirtazapine) was not mutagenic or clastogenic and did not induce general DNA damage as determined in several genotoxicity tests: Ames test, in vitro gene mutation assay in Chinese hamster V 79 cells, in vitro sister chromatid exchange assay in cultured rabbit lymphocytes, in vivo bone marrow micronucleus test in rats, and unscheduled DNA synthesis assay in HeLa cells.

Impairment of Fertility

In a fertility study in rats, REMERON™ (mirtazapine) was given at doses up to 100 mg/kg (20 times the maximum recommended human dose (MRHD) on a mg/m^2 basis), respectively), have revealed no evidence of teratogenic effects. However, in rats, there was an increase in post-implantation losses in dams treated with REMERON™ (mirtazapine). There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of these deaths is not known. These effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m^2 basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REMERON™ (mirtazapine) Tablets are administered to nursing women.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Approximately 190 elderly individuals (≥65 years of age) participated in clinical studies with REMERON™ (mirtazapine). No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering REMERON™ to elderly patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 16 percent of the 453 patients who received REMERON™ (mirtazapine) in U.S. 6-week controlled clinical trials discontinued treatment due to an adverse experience, compared to 7 percent of 361 placebo-treated patients in those studies. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Common Adverse Events Associated with Discontinuation of Treatment in 6-Week U.S. REMERON™ Trials

Adverse Event	Percentage of Patients Discontinuing with Adverse Event	
	REMERON™ (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Commonly Observed Adverse Events in U.S. Controlled Clinical Trials

The most commonly observed adverse events associated with the use of REMERON™ (mirtazapine) (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (REMERON™ incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of REMERON™ in 6-Week U.S. Trials

Adverse Event	Percentage of Patients Reporting Adverse Event	
	REMERON™ (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

Adverse Events Occurring at an Incidence of 1% or More Among REMERON™ Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among REMERON™ (mirtazapine)-treated patients who participated in short-term U.S. placebo-controlled trials in which patients were dosed in a range of 5 to 60 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

INCIDENCE OF ADVERSE CLINICAL EXPERIENCES[1] (≥1%) IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	REMERON™ (n=453)	Placebo (n=361)
Body as a Whole		
Asthenia	8%	5%
Flu Syndrome	5%	3%
Back Pain	2%	1%
Digestive System		
Dry Mouth	25%	15%
Increased Appetite	17%	2%
Constipation	13%	7%
Metabolic and Nutritional Disorders		
Weight Gain	12%	2%
Peripheral Edema	2%	1%
Edema	1%	0%
Musculoskeletal System		
Myalgia	2%	1%
Nervous System		
Somnolence	54%	18%
Dizziness	7%	3%
Abnormal Dreams	4%	1%
Thinking Abnormal	3%	1%
Tremor	2%	1%
Confusion	2%	0%
Respiratory System		
Dyspnea	1%	0%
Urogenital System		
Urinary Frequency	2%	1%

[1] Events reported by at least 1% of patients treated with REMERON™ (mirtazapine) are included, except the following events which had an incidence on placebo ≥REMERON™: headache, infection, pain, chest pain, palpitation, tachycardia, postural hypotension, nausea, dyspepsia, diarrhea, flatulence, insomnia, nervousness, libido decreased, hypertonia, pharyngitis, rhinitis, sweating, amblyopia, tinnitus, taste perversion.

ECG Changes

In an analysis of ECGs obtained in U.S. placebo-controlled clinical trials, REMERON™ (mirtazapine) and placebo-treated patients had a similar incidence of abnormal changes from baseline at 6–8 weeks of approximately 3%. The abnormalities were generally not considered clinically significant.

Other Adverse Events Observed During the Premarketing Evaluation of REMERON™

During its premarketing assessment, multiple doses of REMERON™ (mirtazapine) were administered to 2,796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2,796 patients exposed to multiple doses of REMERON™ who experienced an event of the type cited on at least one occasion while receiving REMERON™. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or

excessively specific so as to be uninformative, and those events for which a drug cause was very remote.

It is important to emphasize that, although the events reported occurred during treatment with REMERON™, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Only those events not already listed in the previous table appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

Body as a Whole: *frequent:* malaise, abdominal pain, abdominal syndrome acute; *infrequent:* chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; *rare:* cellulitis, chest pain substernal.

Cardiovascular System: *frequent:* hypertension, vasodilatation; *infrequent:* angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; *rare:* atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure.

Digestive System: *frequent:* vomiting, anorexia; *infrequent:* eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; *rare:* tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System: *rare:* goiter, hypothyroidism.

Hemic and Lymphatic System: *rare:* lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders: *frequent:* thirst; *infrequent:* dehydration, weight loss; *rare:* gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus.

Musculoskeletal System: *frequent:* myasthenia, arthralgia; *infrequent:* arthritis, tenosynovitis; *rare:* pathological fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis.

Nervous System: *frequent:* hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; *infrequent:* ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction; *rare:* aphasia, nystagmus, akathisia, stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

Respiratory System: *frequent:* cough increased, sinusitis; *infrequent:* epistaxis, bronchitis, asthma, pneumonia; *rare:* asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages: *frequent:* pruritus, rash; *infrequent:* acne exfoliative dermatitis, dry skin, herpes simplex, alopecia; *rare:* urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses: *infrequent:* eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; *rare:* blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: *frequent:* urinary tract infection; *infrequent:* kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence; *rare:* polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

REMERON™ (mirtazapine) Tablets are not a controlled substance.

Physical and Psychological Dependence

REMERON™ (mirtazapine) has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of mirtazapine misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

There is very limited experience with REMERON™ (mirtazapine) overdose. In premarketing clinical studies, there were eight reports of mirtazapine overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking REMERON™ Tablets was in combination with amitriptyline and chlorprothixene in a non-U.S. clinical study. Based on plasma levels, the REMERON™ dose taken was 30–45 mg, while plasma levels of amitriptyline and chlorprothixene were found to be at toxic levels. All other premarketing overdose cases resulted in full recovery. Signs and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia. There were no reports of ECG abnormalities, coma or convulsions following overdose with REMERON™ alone.

Overdose Management

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. There are no specific antidotes for REMERON™ (mirtazapine). If the patient is unconscious, establish and maintain an airway to ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be considered. Activated charcoal should also be considered in treatment of overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

Initial Treatment

The recommended starting dose for REMERON™ (mirtazapine) is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the antidepressant efficacy of REMERON™, the effective dose range was generally 15–45 mg/day. While the relationship between dose and antidepressant response for REMERON™ has not been adequately explored, patients not responding to the initial 15 mg dose may benefit from dose increases up to a maximum of 45 mg/day. REMERON™ has an elimination half-life of approximately 20–40 hours; therefore, dose changes should not be made at intervals of less than one to two weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose.

Elderly and Patients with Renal or Hepatic Impairment

The clearance of mirtazapine is reduced in elderly patients and in patients with moderate to severe renal or hepatic impairment. Consequently, the prescriber should be aware that plasma mirtazapine levels may be increased in these patient groups, compared to levels observed in younger adults without renal or hepatic impairment (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY).

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the depressed patient should be treated with REMERON™ (mirtazapine). It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown.

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with REMERON™ (mirtazapine). In addition, at least 14 days should be allowed after stopping REMERON™ before starting an MAOI.

HOW SUPPLIED

REMERON™ (mirtazapine) Tablets are supplied as:

15 mg Tablets—oval, scored, yellow, coated, with "Organon" embossed on one side and "TZ3" on the other side.

Bottles of 30	NDC# 0052-0105-30
Unit Dose, Box of 100	NDC# 0052-0105-90*

30 mg Tablets—oval, scored, red-brown, coated, with "Organon" embossed on one side and "TZ5" on the other side.

Bottles of 30	NDC# 0052-0107-30
Unit Dose, Box of 100	NDC# 0052-0107-90*

* Unit dose packs are provided as a blisterpack with 10 strips, each of which contains 10 tablets.

Store at controlled Room Temperature 20°–25°C (68°–77°F)

Dispense in a tight, light resistant container.

Caution: Federal law prohibits dispensing without prescription.

Organon
Manufactured for Organon Inc.
West Orange, NJ 07052
by N.V.Organon, OSS, Holland

Shown in Product Identification Guide, page 326

REVERSOL® R

(edrophonium chloride) injection, USP

HOW SUPPLIED

10 mg/mL: 10 mL Multiple Dose Vials-boxes of 25-NDC-0052-0466-34

SUCCINYLCHOLINE CHLORIDE INJECTION, USP R

HOW SUPPLIED

20 mg/mL: 10 mL vials-boxes of 25-NDC-0052-0445-10

TICE® BCG R

BCG VACCINE USP
(for Intravesical or Percutaneous use)

DESCRIPTION

TICE® BCG, a BCG Vaccine for intravesical or percutaneous use, is an attenuated, live culture preparation of the Bacillus of Calmette and Guerin (BCG) strain *Mycobacterium bovis*.[1] The TICE strain was developed at the University of Illinois from a strain originated at the Pasteur Institute.

The medium in which the BCG organism is grown for preparation of the freeze-dried cake is composed of the following ingredients: glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, and iron ammonium citrate. The final preparation prior to freeze-drying also contains lactose. The freeze-dried BCG preparation is delivered in glass-sealed ampules, each containing 1 to 8×10^8 colony forming units (CFU) of TICE BCG which is equivalent to approximately 50 mg wet weight.

No preservatives have been added.

CLINICAL PHARMACOLOGY

Intravesical Use for Carcinoma In Situ of the Bladder. TICE BCG induces a granulomatous reaction at the local site of administration.[2] Intravesical TICE BCG has been used as a therapy for and prophylaxis against recurrent tumors in patients with carcinoma in situ (CIS) of the bladder. The precise mechanism of action is unknown. A variety of different treatment regimens have been used with the TICE[3–6] and other BCG substrains.[7–12]

An evaluation of intravesical administration of TICE BCG in patients with carcinoma in situ of the urinary bladder was recently completed. Bladder cancer patients were identified who had been treated with TICE BCG under six different Investigational New Drug (IND) applications in which the most important shared aspect was the use of an induction plus maintenance schedule. Comparison of demographic data between the six INDs revealed uniformity. Among these six studies were 119 evaluable patients who received intravesical treatment of CIS of the bladder. Patients with biopsy-proven CIS received TICE BCG (50 mg; $1–8 \times 10^8$ CFU) intravesically, once weekly for at least 6 weeks and once monthly thereafter for up to 12 months. A longer maintenance was given in some cases. Follow-up cystoscopies were performed at 3 month intervals, as were urine cytologies for most patients (71 of 119). Urine cytology was obtained at the time of the 1989 follow-up for all patients who responded to TICE BCG *treatment, (CR and CRNC, see below).* The median time post treatment for these follow-up cytologies was 47 months.

The study population consisted of 153 patients; 132 males, 19 females and 2 unidentified as to gender. Thirty patients lacking baseline documentation of CIS and 4 patients lost to follow-up were not evaluable for treatment response. Therefore, 119 patients with biopsy or cystoscopy proven CIS prior to TICE BCG administration were available for efficacy evaluation. Some of these patients had undergone transurethral resection (TUR) one or more weeks prior to BCG, primarily for the treatment of papillomatous disease. The mean age for the CIS population was 68.8 ± 9.7 years s.d. (range: 38–97 years).

Sixty-three evaluable patients had received intravesical chemotherapy treatment for their bladder malignancy prior to TICE BCG treatment and had been diagnosed as treatment failures. The treatment had been as follows: thiotepa (30), mitomycin C (10), doxorubicin (1), mitomycin C and thiotepa (14), doxorubicin and thiotepa (1), doxorubicin and mitomycin C (1), thiotepa, mitomycin C and doxorubicin (2), interferon (1), interferon and thiotepa (1), cyclophosphamide IV (1), and cisplatin and thiotepa (1).

For the 119 patients with biopsy or cystoscopy proven CIS, the TICE BCG induction dosage consisted of a mean of 6.6 instillations (± 1.5 standard error of the mean). These patients also received a mean of 10.0 maintenance instillations after completing the induction phase. Twenty patients (16.8%) required TICE BCG reinduction at some point in the

Continued on next page

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WARNINGS
SPECTAZOLE is not for ophthalmic use.

PRECAUTIONS
General: If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued.
For external use only. Avoid introduction of SPECTAZOLE Cream into the eyes.
Carcinogenicity Studies: Long-term animal studies to determine carcinogenic potential have not been performed.
Fertility (Reproduction): Oral administration of econazole nitrate in rats has been reported to produce prolonged gestation. Intravaginal administration in humans has not shown prolonged gestation or other adverse reproductive effects attributable to econazole nitrate therapy.
Pregnancy: Pregnancy Category C. Econazole nitrate has not been shown to be teratogenic when administered orally to mice, rabbits or rats. Fetotoxic or embryotoxic effects were observed in Segment I oral studies with rats receiving 10 to 40 times the human dermal dose. Similar effects were observed in Segment II or Segment III studies with mice, rabbits and/or rats receiving oral doses 80 or 40 times the human dermal dose.
Econazole nitrate should be used in the first trimester of pregnancy only when the physician considers it essential to the welfare of the patient. The drug should be used during the second and third trimesters of pregnancy only if clearly needed.
Nursing Mothers: It is not known whether econazole nitrate is excreted in human milk. Following oral administration of econazole nitrate to lactating rats, econazole and/or metabolites were excreted in milk and were found in nursing pups. Also, in lactating rats receiving large oral doses (40 or 80 times the human dermal dose), there was a reduction in postpartum viability of pups and survival to weaning; however, at these high doses, maternal toxicity was present and may have been a contributing factor. Caution should be exercised when econazole nitrate is administered to a nursing woman.

ADVERSE REACTIONS
During clinical trials, approximately 3% of patients treated with econazole nitrate 1% cream reported side effects thought possibly to be due to the drug, consisting mainly of burning, itching, stinging and erythema. One case of pruritic rash has also been reported.

OVERDOSE
Overdosage of econazole nitrate in humans has not been reported to date. In mice, rats, guinea pigs and dogs, the oral LD 50 values were found to be 462, 668, 272, and > 160 mg/kg, respectively.

DOSAGE AND ADMINISTRATION
Sufficient SPECTAZOLE Cream should be applied to cover affected areas once daily in patients with tinea pedis, tinea cruris, tinea corporis, and tinea versicolor, and twice daily (morning and evening) in patients with cutaneous candidiasis.
Early relief of symptoms is experienced by the majority of patients and clinical improvement may be seen fairly soon after treatment is begun; however, candidal infections and tinea cruris and corporis should be treated for two weeks and tinea pedis for one month in order to reduce the possibility of recurrence. If a patient shows no clinical improvement after the treatment period, the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatment.

HOW SUPPLIED
SPECTAZOLE (econazole nitrate 1%) Cream is supplied in tubes of 15 grams (NDC 0062-5460-02), 30 grams (NDC 0062-5460-01), and 85 grams (NDC 0062-5460-03).
Store SPECTAZOLE Cream below 86°F.
Revised March 1994 631-10-331-8
Shown in Product Identification Guide, page 326

For EMERGENCY telephone numbers, consult the **Manufacturers Index.**

Paddock Laboratories, Inc.
3940 QUEBEC AVENUE NORTH
MINNEAPOLIS, MN 55427

Direct Inquiries to:
(800) 328-5113
For Medical Information Contact:
Medical Department
(800) 328-5113

ACTIDOSE with SORBITOL™ OTC
[*act'i'-dose*]
(Activated Charcoal with Sorbitol Suspension)

DESCRIPTION
Actidose with Sorbitol is supplied in bottles and tubes. Each 120 mL package contains 25 grams of activated charcoal in suspension and 48 grams of sorbitol. Each 240 mL package contains 50 grams of activated charcoal in suspension and 96 grams of sorbitol. Each milliliter contains 208 mg (0.208 gram) activated in charcoal and 400 mg (0.4 gram) sorbitol.

HOW SUPPLIED
25 g unit-of-use bottle NDC 0574-0120-04
50 g unit-of-use bottle NDC 0574-0120-08
25 g unit-of-use tube NDC 0574-0120-74
50 g unit-of-use tube NDC 0574-0120-76

ACTIDOSE-AQUA™ OTC
[*act'i'dose a-qua*]
(Activated Charcoal Suspension)

DESCRIPTION
Actidose-Aqua is supplied in bottles and tubes. Each 72 mL package contains 15 grams of activated charcoal in suspension, each 120 mL package contains 25 grams of activated charcoal in suspension and each 240 mL package contains 50 grams of activated charcoal in suspension. Each milliliter contains 208 mg (0.208 gram) activated charcoal.

HOW SUPPLIED
15 g unit-of-use bottle NDC 0574-0120-25
25 g unit-of-use bottle NDC 0574-0120-04
50 g unit-of-use bottle NDC 0574-0120-08
25 g unit-of-use tube NDC 0574-0120-74
50 g unit-of-use tube NDC 0574-0120-76

CLINDA-DERM™ ℞
[*clī n'dă-dĕrm*]
(Clindamycin Phosphate Topical Solution, USP, 1%)

DESCRIPTION
Clindamycin phosphate is a water-soluble ester of a semisynthetic antibiotic produced from lincomycin. Clinda-Derm™ contains clindamycin phosphate equivalent to 10 mEq of clindamycin per ml. in a clear solution vehicle of 51.5% v/v isopropyl alcohol, propylene glycol, sodium hydroxide, and purified water.

HOW SUPPLIED
Bottles of 2 fl. oz. (60 ml.) Store at controlled room temperature 15–30°C (59–86°F)
NDC 0574-0016-02

DIABE-TUSS DM™ Syrup OTC
(Dextromethorphan Hydrobromide USP)

DESCRIPTION
Cherry flavored cough suppressant in an alcohol-free, sugar-free, dye-free base. Each teaspoonful (5 mL) contains dextromethorphan hydrobromide USP 15 mg.

INDICATIONS
Temporarily relieves cough due to minor throat and bronchial irritation associated with the common cold.

DOSAGE AND ADMINISTRATION
(See dosage below. Do not exceed four doses in a 24-hour period):
Adults and children over 12 years: 2 teaspoonfuls every 6 hours.
Children 6 to 12 years: 1 teaspoonful every 6 hours.
Children 2 to 6 years: ½ teaspoonful every 6 hours.
Children under 2: Consult a doctor.

HOW SUPPLIED
DIABE-TUSS DM is available in 118 mL (4 Fl Oz) bottles.
NDC: 0574-0022-04

ERYTHRA-DERM™ ℞
(Erythromycin Topical Solution USP, 2%)

DESCRIPTION
Erythromycin is an antibiotic produced from a strain of *Streptomyces erythraeus*. It is basic and readily forms salts with acids. ERYTHRA-DERM contains 20 mg/ml erythromycin base in a clear solution vehicle of 66 percent alcohol, propylene glycol and citric acid.

HOW SUPPLIED
Bottles of 2 fl. oz. (60 ml). Store at controlled room temperature (59°F–86°F). NDC 0574-0014-02

GLUTOSE 15™ OTC
GLUTOSE 45™
(Oral Glucose Gel)

DESCRIPTION
Glutose gel is a lemon-flavored, dye-free oral glucose gel for treatment of insulin reaction or hypoglycemia. Glutose gel contains Dextrose (d-Glucose) 40%.

HOW SUPPLIED
Glutose 15: 3 x 15g unit-of-use tubes per package NDC 0574-0069-30
Glutose 45: 1 x 45g multi-use tube per package NDC 0574-0069-45

GLUTOSE™ Tablets OTC
(Oral Glucose Chewable Tablets)

DESCRIPTION
Glutose tablets are lemon-flavored chewable tablets for treatment of insulin reaction or hypoglycemia. Each tablet contains 5 grams of Dextrose.

HOW SUPPLIED
Box of 12 tablets NDC 0574-0068-12

NYSTATIN PADDOCK™
NYSTATIN, USP ℞
For Extemporaneous Preparation of Oral Suspension

DESCRIPTION
Nystatin USP is an antifungal antibiotic obtained from *Streptomyces noursei*. It is known to be a mixture, but the composition has not been completely elucidated. Nystatin A_1 is closely related to amphotericin B. Each is a macrocyclic lactone containing a ketal ring, an all-trans polyene system, and a mycosamine (3-amino-3-deoxy-rhamnose) moiety.
Nystatin USP is a ready-to-use, non-sterile powder for oral administration which contains no excipients or preservatives. It is available in containers of 50 million, 150 million, 500 million, 1 billion, 2 billion, and 5 billion units. Each mg contains not less than 5,000 units.

HOW SUPPLIED

Product Code (NDC)	Size (units)	Approx. Weight (grams)
0574-0404-05	50 million	8.3 – 10
0574-0404-15	150 million	25 – 30
0574-0404-50	500 million	83 – 100
0574-0404-01	1 billion	167 – 200
0574-0404-02	2 billion	333 – 400
0574-0404-00	5 billion	833 – 1,000

Storage: Store in a refrigerator. 2°–8°C (36°–46°F) protect from light.
07-95

NYSTOP™ ℞
Nystatin Topical Powder USP
For topical use only.
Not for ophthalmic use.

DESCRIPTION
Nystatin Topical Powder USP is for dermatologic use.
Nystatin Topical Powder USP provides, in each gram, 100,000 USP nystatin units dispersed in talc.

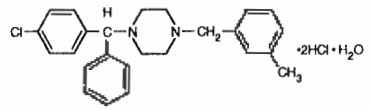
Pfizer Inc—Cont.

562 Atarax® (hydroxyzine HCl) Tablets, 50 mg
563 Atarax® (hydroxyzine HCl) Tablets, 100 mg
275 Cardura® (doxazosin mesylate) Tablets, 1 mg
276 Cardura® (doxazosin mesylate) Tablets, 2 mg
277 Cardura® (doxazosin mesylate) Tablets, 4 mg
278 Cardura® (doxazosin mesylate) Tablets, 8 mg
393 Diabinese® (chlorpropamide) Tablets 100 mg
394 Diabinese® (chlorpropamide) Tablets 250 mg
341 Diflucan® (fluconazole) Tablets 50 mg
342 Diflucan® (fluconazole) Tablets 100 mg
350 Diflucan® (fluconazole) Tablets 150 mg
343 Diflucan® (fluconazole) Tablets 200 mg
322 Feldene® (piroxicam) Capsules 10 mg
323 Feldene® (piroxicam) Capsules 20 mg
143 Geocillin® (carbenicillin indanyl sodium) Tablets equivalent to 382 mg carbenicillin
411 Glucotrol® (glipizide) Tablets 5 mg
412 Glucotrol® (glipizide) Tablets 10 mg
155 Glucotrol XL™ (glipizide) Extended Release Tablets 5 mg GITS
156 Glucotrol XL™ (glipizide) Extended Release Tablets 10 mg GITS
254 Marax® (ephedrine sulfate, 25 mg; theophylline, 130 mg; and Atarax® [hydroxyzine HCl], 10 mg) Tablets
431 Minipress® (prazosin HCl) Capsules 1 mg
437 Minipress® (prazosin HCl) Capsules 2 mg
438 Minipress® (prazosin HCl) Capsules 5 mg
430 Minizide® 1 Capsules (1 mg prazosin HCl and 0.5 mg polythiazide)
432 Minizide® 2 Capsules (2 mg prazosin HCl and 0.5 mg polythiazide)
436 Minizide® 5 Capsules (5 mg prazosin HCl and 0.5 mg polythiazide)
571 Navane® (thiothixene) Capsules, 1 mg
572 Navane® (thiothixene) Capsules, 2 mg
573 Navane® (thiothixene) Capsules, 5 mg
574 Navane® (thiothixene) Capsules, 10 mg
577 Navane® (thiothixene) Capsules, 20 mg
152 Norvasc® (amlodipine besylate) Tablets 2.5 mg
153 Norvasc® (amlodipine besylate) Tablets 5 mg
154 Norvasc® (amlodipine besylate) Tablets 10 mg
260 Procardia® (nifedipine) Capsules, 10 mg
261 Procardia® (nifedipine) Capsules, 20 mg
265 Procardia XL® (nifedipine) Extended Release Tablets, 30 mg GITS
266 Procardia XL® (nifedipine) Extended Release Tablets, 60 mg GITS
267 Procardia XL® (nifedipine) Extended Release Tablets, 90 mg GITS
534 Sinequan® (doxepin HCl) Capsules 10 mg
535 Sinequan® (doxepin HCl) Capsules 25 mg
536 Sinequan® (doxepin HCl) Capsules 50 mg
539 Sinequan® (doxepin HCl) Capsules 75 mg
538 Sinequan® (doxepin HCl) Capsules 100 mg
537 Sinequan® (doxepin HCl) Capsules 150 mg
035 Spectrobid® (bacampicillin HCl) Tablets, 400 mg, equivalent to 280 mg ampicillin
159 TAO® (troleandomycin) Capsules, 250 mg
092 Urobiotic®-250 (oxytetracycline HCl 250 mg with sulfamethizole 250 mg and phenazopyridine 50 mg) Capsules
094 Vibramycin® Hyclate (doxycycline hyclate) Capsules 50 mg
095 Vibramycin® Hyclate (doxycycline hyclate) Capsules 100 mg
099 Vibra-Tabs® (doxycycline hyclate) Film Coated Tablets 100 mg
541 Vistaril® (hydroxyzine pamoate) Capsules 25 mg
542 Vistaril® (hydroxyzine pamoate) Capsules 50 mg
543 Vistaril® (hydroxyzine pamoate) Capsules 100 mg
305 Zithromax® (azithromycin) Capsules 250 mg
305 Zithromax® (azithromycin) Z-PAK™ (6 × 250-mg Capsules)
308 Zithromax® (azithromycin) 600 mg Tablets
490 Zoloft™ (sertraline HCl) Tablets, 50 mg
491 Zoloft™ (sertraline HCl) Tablets, 100 mg
550 Zyrtec™ (cetirizine hydrochloride) Tablets 5 mg
551 Zyrtec™ (cetirizine hydrochloride) Tablets 10 mg

ANTIVERT® TABLETS ℞
[ăn 'tĭ-vert ″]
(12.5 mg meclizine HCl)
ANTIVERT®/25 TABLETS ℞
(25 mg meclizine HCl)
ANTIVERT®/50 TABLETS ℞
(50 mg meclizine HCl)

DESCRIPTION

Chemically, Antivert (meclizine HCl) is 1-(*p*-chloro-α-phenylbenzyl)-4-(*m*-methylbenzyl) piperazine dihydrochloride monohydrate.



Inert ingredients for the tablets are: dibasic calcium phosphate; magnesium stearate; polyethylene glycol; starch; sucrose. The 12.5 mg tablets also contain: Blue 1. The 25 mg tablets also contain: Yellow 6 Lake; Yellow 10 Lake. The 50 mg tablets also contain: Blue 1 Lake; Yellow 10 Lake.

ACTIONS

Antivert is an antihistamine which shows marked protective activity against nebulized histamine and lethal doses of intravenously injected histamine in guinea pigs. It has a marked effect in blocking the vasodepressor response to histamine, but only a slight blocking action against acetylcholine. Its activity is relatively weak in inhibiting the spasmogenic action of histamine on isolated guinea pig ileum.

INDICATIONS

Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:
Effective: Management of nausea and vomiting, and dizziness associated with motion sickness.
Possibly Effective: Management of vertigo associated with diseases affecting the vestibular system.
Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS

Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.
Patients should avoid alcoholic beverages while taking this drug. Due to its potential anticholinergic action, this drug should be used with caution in patients with asthma, glaucoma, or enlargement of the prostate gland.

USAGE IN CHILDREN
Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in children under 12 years of age.
USAGE IN PREGNANCY
Pregnancy Category B. Reproduction studies in rats have shown cleft palates at 25–50 times the human dose. Epidemiological studies in pregnant women, however, do not indicate that meclizine increases the risk of abnormalities when administered during pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote. Nevertheless, meclizine, or any other medication, should be used during pregnancy only if clearly necessary.

ADVERSE REACTIONS

Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

DOSAGE AND ADMINISTRATION

Vertigo:
For the control of vertigo associated with diseases affecting the vestibular system, the recommended dose is 25 to 100 mg daily, in divided dosage, depending upon clinical response.
Motion Sickness:
The initial dose of 25 to 50 mg of Antivert should be taken one hour prior to embarkation for protection against motion sickness. Thereafter, the dose may be repeated every 24 hours for the duration of the journey.

HOW SUPPLIED

Antivert—12.5 mg tablets: bottles of 100 (NDC 0662-2100-66), 1000 (NDC 0662-2100-82).
Antivert/25—25 mg tablets: bottles of 100 (NDC 0662-2110-66), 1000 (NDC 0662-2110-82).
Antivert/50—50 mg tablets: bottles of 100 (NDC 0662-2140-66).

69-2148-37-7

Shown in Product Identification Guide, page 327

ATARAX® ℞
[ăt 'ă-raks ″]
(hydroxyzine hydrochloride)
TABLETS AND SYRUP

DESCRIPTION

Hydroxyzine hydrochloride is designated chemically as 1-(p-chlorobenzhydryl) 4-[2-(2-hydroxyethoxy)-ethyl] piperazine dihydrochloride.
Inert ingredients for the tablets are: acacia; carnauba wax; dibasic calcium phosphate; gelatin; lactose; magnesium stearate; precipitated calcium carbonate; shellac; sucrose; talc; white wax. The 10 mg tablets also contain: sodium hydroxide; starch; titanium dioxide; Yellow 6 Lake. The 25 mg tablets also contain: starch, velo dark green. The 50 mg tablets also contain: starch; velo yellow. The 100 mg tablets also contain: alginic acid; Blue 1; polyethylene glycol; Red 3.
The inert ingredients for the syrup are: alcohol; menthol; peppermint oil; sodium benzoate; spearmint oil; sucrose; water.

CLINICAL PHARMACOLOGY

Atarax is unrelated chemically to the phenothiazines, reserpine, meprobamate, or the benzodiazepines.
Atarax is not a cortical depressant, but its action may be due to a suppression of activity in certain key regions of the subcortical area of the central nervous system. Primary skeletal muscle relaxation has been demonstrated experimentally. Bronchodilator activity, and antihistaminic and analgesic effects have been demonstrated experimentally and confirmed clinically. An antiemetic effect, both by the apomorphine test and the veriloid test, has been demonstrated. Pharmacological and clinical studies indicate that hydroxyzine in therapeutic dosage does not increase gastric secretion or acidity and in most cases has mild antisecretory activity. Hydroxyzine is rapidly absorbed from the gastrointestinal tract and Atarax's clinical effects are usually noted within 15 to 30 minutes after oral administration.

INDICATIONS

For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested.
Useful in the management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatoses, and in histamine-mediated pruritus.
As a sedative when used as premedication and following general anesthesia, **Hydroxyzine may potentiate meperidine (Demerol®) and barbiturates,** so their use in pre-anesthetic adjunctive therapy should be modified on an individual basis. Atropine and other belladonna alkaloids are not affected by the drug. Hydroxyzine is not known to interfere with the action of digitalis in any way and it may be used concurrently with this agent.
The effectiveness of hydroxyzine as an antianxiety agent for long term use, that is more than 4 months, has not been assessed by systematic clinical studies. The physician should

reassess periodically the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat and mouse at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate to establish safety in early pregnancy. Until such data are available, hydroxyzine is contraindicated in early pregnancy.
Hydroxyzine is contraindicated for patients who have shown a previous hypersensitivity to it.

WARNINGS

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since many drugs are so excreted, hydroxyzine should not be given to nursing mothers.
For Tablets Only: This product is manufactured with 1,1,1-trichloroethane, a substance which harms public health and the environment by destroying ozone in the upper atmosphere.

PRECAUTIONS

THE POTENTIATING ACTION OF HYDROXYZINE MUST BE CONSIDERED WHEN THE DRUG IS USED IN CONJUNCTION WITH CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS, NON-NARCOTIC ANALGESICS AND BARBITURATES. Therefore when central nervous system depressants are administered concomitantly with hydroxyzine their dosage should be reduced. Since drowsiness may occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery while taking Atarax. Patients should be advised against the simultaneous use of other CNS depressant drugs, and cautioned that the effect of alcohol may be increased.

ADVERSE REACTIONS

Side effects reported with the administration of Atarax (hydroxyzine hydrochloride) are usually mild and transitory in nature.
Anticholinergic: Dry mouth.
Central Nervous System: Drowsiness is usually transitory and may disappear in a few days of continued therapy or upon reduction of the dose. Involuntary motor activity including rare instances of tremor and convulsions have been reported, usually with doses considerably higher than those recommended. Clinically significant respiratory depression has not been reported at recommended doses.

OVERDOSAGE

The most common manifestation of Atarax overdosage is hypersedation. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken.
If vomiting has not occurred spontaneously, it should be induced. Immediate gastric lavage is also recommended. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated. Hypotension, though unlikely, may be controlled with intravenous fluids and Levophed® (levarterenol), or Aramine® (metaraminol). Do not use epinephrine as Atarax counteracts its pressor action.
There is no specific antidote. It is doubtful that hemodialysis would be of any value in the treatment of overdosage with hydroxyzine. However, if other agents such as barbiturates have been ingested concomitantly, hemodialysis may be indicated. There is no practical method to quantitate hydroxyzine in body fluids or tissue after its ingestion or administration.

DOSAGE

For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested: in adults, 50–100 mg q.i.d.; children under 6 years, 50 mg daily in divided doses and over 6 years, 50–100 mg daily in divided doses.
For use in the management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatoses, and in histamine-mediated pruritus: in adults, 25 mg t.i.d. or q.i.d.; children under 6 years, 50 mg daily in divided doses and over 6 years, 50–100 mg daily in divided doses.
As a sedative when used as a premedication and following general anesthesia: 50–100 mg in adults, and 0.6 mg/kg in children.
When treatment is initiated by the intramuscular route of administration, subsequent doses may be administered orally.
As with all medications, the dosage should be adjusted according to the patient's response to therapy.

SUPPLY

Atarax Tablets
10 mg—orange tablets: 100's (NDC 0049-5600-66), 500's (NDC 0049-5600-73) Unit Dose 10 × 10's (NDC 0049-5600-41), and Unit of Use 40's (NDC 0049-5600-43)
25 mg—green tablets: 100's (NDC 0049-5610-66), 500's (NDC 0049-5610-73) Unit Dose 10 × 10's (NDC 0049-5610-41), and Unit of Use 40's (NDC 0049-5610-43)
50 mg—yellow tablets: 100's (NDC 0049-5620-66), 500's (NDC 0049-5620-73)
100 mg—red tablets: 100's (NDC 0049-5630-66)
Atarax Syrup
10 mg per teaspoon (5 ml): 1 pint bottles (NDC 0049-5590-93)
Alcohol Content—Ethyl Alcohol—0.5% v/v

BIBLIOGRAPHY

Available on request.
69-0618-00-5 Revised Dec. 1993
Shown in Product Identification Guide, page 327

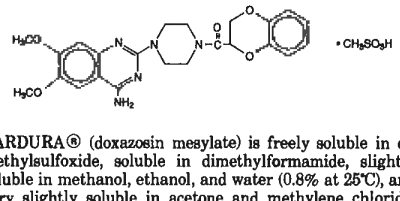
CARDURA®

(doxazosin mesylate)
Tablets

℞

DESCRIPTION

CARDURA® (doxazosin mesylate) is a quinazoline compound that is a selective inhibitor of the alpha$_1$ subtype of alpha adrenergic receptors. The chemical name of doxazosin mesylate is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate. The empirical formula for doxazosin mesylate is $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$ and the molecular weight is 547.6. It has the following structure:



CARDURA® (doxazosin mesylate) is freely soluble in dimethylsulfoxide, soluble in dimethylformamide, slightly soluble in methanol, ethanol, and water (0.8% at 25°C), and very slightly soluble in acetone and methylene chloride. CARDURA® is available as colored tablets for oral use and contains 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) of doxazosin as the free base.
The inactive ingredients for all tablets are: microcrystalline cellulose, lactose, sodium starch glycolate, magnesium stearate and sodium lauryl sulfate. The 2 mg tablet contains D & C yellow 10 and FD & C yellow 6; the 4 mg tablet contains FD & C yellow 6; the 8 mg tablet contains FD & C blue 10 and D & C yellow 10.

CLINICAL PHARMACOLOGY

Pharmacodynamics

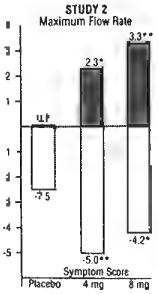
A. *Benign Prostatic Hyperplasia (BPH)*

Benign prostatic hyperplasia (BPH) is a common cause of urinary outflow obstruction in aging males. Severe BPH may lead to urinary retention and renal damage. A static and a dynamic component contribute to the symptoms and reduced urinary flow rate associated with BPH. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component of BPH is associated with an increase in smooth muscle tone in the prostate and bladder neck. The degree of tone in this area is mediated by the alpha$_1$ adrenoceptor, which is present in high density in the prostatic stroma, prostatic capsule and bladder neck. Blockade of the alpha$_1$ receptor decreases urethral resistance and may relieve the obstruction and BPH symptoms. In the human prostate, CARDURA® antagonizes phenylephrine (alpha$_1$ agonist)-induced contractions, *in vitro*, and binds with high affinity to the alpha$_{1c}$ adrenoceptor. The receptor subtype is thought to be the predominant functional type in the prostate. CARDURA® acts within 1–2 weeks to decrease the severity of BPH symptoms and improve urinary flow rate. Since alpha$_1$ adrenoceptors are of low density in the urinary bladder (apart from the bladder neck), CARDURA® should maintain bladder contractility.
The efficacy of CARDURA® was evaluated extensively in over 900 patients with BPH in double-blind, placebo-controlled trials. CARDURA® treatment was superior to placebo in improving patient symptoms and urinary flow rate. Significant relief with CARDURA® was seen as early as one week into the treatment regimen, with CARDURA® treated patients (N=173) showing a significant ($p < 0.01$) increase in maximum flow rate of 0.8 mL/sec compared to a decrease of 0.5 mL/sec in the placebo group (N=41). In long term studies improvement was maintained for up to 2 years of treatment. In 66–71% of patients, improvements above baseline were seen in both symptoms and maximum urinary flow rate.
In three placebo-controlled studies of 14–16 weeks duration obstructive symptoms (hesitation, intermittency, dribbling, weak urinary stream, incomplete emptying of the bladder) and irritative symptoms (nocturia, daytime frequency, urgency, burning) of BPH were evaluated at each visit by patient-assessed symptom questionnaires. The bothersomeness of symptoms was measured with a modified Boyarsky questionnaire. Symptom severity/frequency was assessed using a modified Boyarsky questionnaire or an AUA-based questionnaire. Uroflowmetric evaluations were performed at times of peak (2–6 hours post-dose) and/or trough (24 hours post-dose) plasma concentrations of CARDURA®.
The results from the three placebo-controlled studies (N=609) showing significant efficacy with 4 mg and 8 mg doxazosin are summarized in Table 1. In all three studies, CARDURA® resulted in statistically significant relief of obstructive and irritative symptoms compared to placebo. Statistically significant improvements of 2.3–3.3 mL/sec in maximum flow rate were seen with CARDURA® in Studies 1 and 2, compared to 0.1–0.7 mL/sec with placebo.
[See table 1 below.]
In one fixed dose study (study 2) CARDURA® therapy (4–8 mg, once daily) resulted in a significant and sustained improvement in maximum urinary flow rate of 2.3–3.3 mL/sec (Table 1) compared to placebo (0.1 mL/sec). In this study, the only study in which weekly evaluations were made, significant improvement with CARDURA® vs. placebo was seen after one week. The proportion of patients who responded with a maximum flow rate improvement of ≥ 3 mL/sec was significantly larger with CARDURA® (34–42%) than placebo (13–17%). A significantly greater improvement was also seen in average flow rate with CARDURA® (1.6 mL/sec) than with placebo (0.2 mL/sec). The onset and time course of symptom relief and increased urinary flow from study 1 are illustrated in Figure 1.
[See Figure 1 at bottom of next page.]
In BPH patients (N=450) treated for up to 2 years in open-label studies, CARDURA® therapy resulted in significant improvement above baseline in urinary flow rates and BPH

TABLE 1
SUMMARY OF EFFECTIVENESS DATA IN PLACEBO-CONTROLLED TRIALS

	SYMPTOM SCORE[a]			MAXIMUM FLOW RATE (mL/sec)		
	N	MEAN BASELINE	MEAN[b] CHANGE	N	MEAN BASELINE	MEAN[c] CHANGE
STUDY 1 (Titration to maximum dose of 8 mg)[d]						
Placebo	47	15.6	−2.3	41	9.7	+0.7
CARDURA	49	14.5	−4.9**	41	9.8	+2.9**
STUDY 2 (Titration to fixed dose—14 weeks)[d]						
Placebo	37	20.7	−2.5	30	10.6	+0.1
CARDURA 4 mg	38	21.2	−5.0**	32	9.8	+2.3*
CARDURA 8 mg	42	19.9	−4.2*	36	10.5	+3.3**
Study 3 (Titration to fixed dose—12 weeks)						
Placebo	47	14.9	−4.7	44	9.9	+2.1
CARDURA 4 mg	46	16.6	−6.1*	46	9.6	+2.6

[a] AUA questionnaire (range 0–30) in studies 1 and 3.
Modified Boyarsky Questionnaire (range 7–39) in study 2.
[b] Change is to endpoint.
[c] Change is to fixed-dose efficacy phase, 22–26 hours post-dose for studies 1 and 3 and 2–6 hours post-dose for study 2.
[d] Study in hypertensives with BPH
[e] 36 patients received a dose of 8 mg CARDURA®
*(**) $p < 0.05$ (0.01) compared to placebo mean change.



Continued on next page

Systemic Candida infections: For the treatment of candidemia and disseminated Candida infections, daily doses of 6–12 mg/kg/day have been used in an open, noncomparative study of a small number of children.

Cryptococcal meningitis: For the treatment of acute cryptococcal meningitis, the recommended dosage is 12 mg/kg on the first day, followed by 6 mg/kg once daily. A dosage of 12 mg/kg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10–12 weeks after the cerebrospinal fluid becomes culture negative. For suppression of relapse of cryptococcal meningitis in children with AIDS, the recommended dose of DIFLUCAN is 6 mg/kg once daily.

Dosage In Patients With Impaired Renal Function:

Fluconazole is cleared primarily by renal excretion as unchanged drug. There is no need to adjust single dose therapy for vaginal candidiasis because of impaired renal function. In patients with impaired renal function who will receive multiple doses of DIFLUCAN, an initial loading dose of 50 to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine Clearance (mL/min)	Percent of Recommended Dose
> 50	100%
≤ 50 (no dialysis)	50%
Regular dialysis	100% after each dialysis

These are suggested dose adjustments based on pharmacokinetics following administration of multiple doses. Further adjustment may be needed depending upon clinical condition.

When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance in adults:

$$\text{Males: } \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100mL)}}$$

$$\text{Females: } 0.85 \times \text{above value}$$

Although the pharmacokinetics of fluconazole has not been studied in children with renal insufficiency, dosage reduction in children with renal insufficiency should parallel that recommended for adults. The following formula may be used to estimate creatinine clearance in children.

$$K \times \frac{\text{linear length or height (cm)}}{\text{serum creatinine (mg/100 mL)}}$$

(Where K = 0.55 for children older than 1 year and 0.45 for infants.)

Administration

DIFLUCAN may be administered either orally or by intravenous infusion. DIFLUCAN injection has been used safely for up to fourteen days of intravenous therapy. The intravenous infusion of DIFLUCAN should be administered at a maximum rate of approximately 200 mg/hour, given as a continuous infusion.

DIFLUCAN injections in glass and Viaflex® Plus plastic containers are intended only for intravenous administration using sterile equipment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if the solution is cloudy or precipitated or if the seal is not intact.

Directions for Mixing the Oral Suspension

Prepare a suspension at time of dispensing as follows: tap bottle until all the powder flows freely. To reconstitute, add 24 mL of distilled water or Purified Water (USP) to fluconazole bottle and shake vigorously to suspend powder. Each bottle will deliver 35 mL of suspension. The concentrations of the reconstituted suspensions are as follows:

Fluconazole Content per Bottle	Concentration of Reconstituted Suspension
350 mg	10 mg/mL
1400 mg	40 mg/mL

Note: Shake oral suspension well before using. Store reconstituted suspension between 86°F (30°C) and 41°F (5°C) and discard unused portion after 2 weeks. Protect from freezing.

Directions for IV Use of DIFLUCAN in Viaflex® Plus Plastic Containers

Do not remove unit from overwrap until ready for use. The overwrap is a moisture barrier. The inner bag maintains the sterility of the product.

CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

To Open

Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. After removing overwrap, check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

DO NOT ADD SUPPLEMENTARY MEDICATION.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

HOW SUPPLIED

DIFLUCAN® Tablets: Pink trapezoidal tablets containing 50, 100 or 200 mg of fluconazole are packaged in bottles or unit dose blisters. The 150 mg fluconazole tablets are pink and oval shaped, packaged in a single dose unit blister.

DIFLUCAN® Tablets are supplied as follows:

DIFLUCAN® 50 mg Tablets: Engraved with DIFLUCAN® and 50 on the front and ROERIG on the back.

NDC 0049-3410-30 Bottles of 30

DIFLUCAN® 100 mg Tablets: Engraved with DIFLUCAN® and 100 on the front and ROERIG on the back.

NDC 0049-3420-30 Bottles of 30

NDC 0049-3420-41 Unit dose package of 100

DIFLUCAN® 150 mg Tablets: Engraved with DIFLUCAN® and 150 mg on the front and ROERIG on the back.

NDC 0049-3500-79 Unit dose package of 1

DIFLUCAN® 200 mg Tablets: Engraved with DIFLUCAN® and 200 on the front and ROERIG on the back.

NDC 0049-3430-30 Bottles of 30

NDC 0049-3430-41 Unit dose package of 100

Storage: Store tablets below 86°F (30°C).

DIFLUCAN® for Oral Suspension: DIFLUCAN® for oral suspension is supplied as an orange-flavored powder to provide 35 mL per bottle as follows:

NDC 0049-3440-19 Fluconazole 350 mg per bottle

NDC 0049-3450-19 Fluconazole 1400 mg per bottle

Storage: Store dry powder below 86°F (30°C). Store reconstituted suspension between 86°F (30°C) and 41°F (5°C) and discard unused portion after 2 weeks. Protect from freezing.

DIFLUCAN® Injections: DIFLUCAN® injections for intravenous infusion administration are formulated as sterile iso-osmotic solutions containing 2 mg/mL of fluconazole. They are supplied in glass bottles or in Viaflex® Plus plastic containers containing volumes of 100 mL or 200 mL affording doses of 200 mg and 400 mg of fluconazole, respectively. DIFLUCAN® injections in Viaflex® Plus plastic containers are available in both sodium chloride and dextrose diluents.

DIFLUCAN® Injections in Glass Bottles:

NDC 0049-3371-26 Fluconazole in Sodium Chloride Diluent 200 mg/100 mL × 6

NDC 0049-3372-26 Fluconazole in Sodium Chloride Diluent 400 mg/200 mL × 6

Storage: Store between 86°F (30°C) and 41°F (5°C). Protect from freezing.

DIFLUCAN® Injections in Viaflex® Plus Plastic Containers:

NDC 0049-3435-26 Fluconazole in Sodium Chloride Diluent 200 mg/100 mL × 6

NDC 0049-3436-26 Fluconazole in Sodium Chloride Diluent 400 mg/200 mL × 6

NDC 0049-3437-26 Fluconazole in Dextrose Diluent 200 mg/100 mL × 6

NDC 0049-3438-26 Fluconazole in Dextrose Diluent 400 mg/200 mL × 6

Storage: Store between 77°F (25°C) and 41°F (5°C). Brief exposure up to 104°F (40°C) does not adversely affect the product. Protect from freezing.

69-4526-00-3 Revised May 1996

Shown in Product Identification Guide, pages 327 and 328

EMETE-CON®

℞

[ă-mĕt 'ă-kŏn ″]

(benzquinamide hydrochloride)

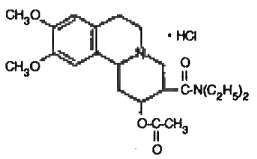
For Intramuscular and Intravenous Use

DESCRIPTION

Benzquinamide is a non-amine-depleting benzoquinolizine derivative, chemically unrelated to the phenothiazines and to other antiemetics.

Chemically, Emete-con (benzquinamide hydrochloride) is N,N-diethyl-1,3,4,6,7,11b-hexahydro-2-hydroxy-9,10-dimethoxy-2H-benzo-[a]quinolizine-3-carboxamide acetate hydrochloride. The empirical formula is $C_{22}H_{32}N_2O_5 \cdot HCl$ and the molecular weight is 441.

[See chemical structure at top of next column.]



Emete-con for injection contains benzquinamide hydrochloride equivalent to 50 mg/vial of benzquinamide. When reconstituted with 2.2 ml of proper diluent, each vial yields 2 ml of a solution containing benzquinamide hydrochloride equivalent to 25 mg/ml of benzquinamide. When reconstituted this product maintains its potency for 14 days at room temperature.

ACTIONS

Benzquinamide HCl exhibited antiemetic, antihistaminic, mild anticholinergic and sedative action in animals. Studies conducted in dogs and human volunteers have demonstrated suppression of apomorphine-induced vomiting; however, relevance to clinical efficacy has not been established. The mechanism of action in humans is unknown. The onset of antiemetic activity in humans usually occurs within 15 minutes.

Benzquinamide metabolism has been studied in animals and in man. In both species, 5-10% of an administered dose is excreted unchanged in the urine. The remaining drug undergoes metabolic transformation in the liver by at least three pathways to a spectrum of metabolites which are excreted in the urine and in the bile, from which the more polar metabolites are not reabsorbed but are excreted in the feces. The half-life in plasma of Emete-con is about 40 minutes. More than 95% of an administered dose was excreted within 72 hours in animal studies using C14-labeled benzquinamide. In blood, benzquinamide is about 58% bound to plasma protein.

INDICATIONS

Emete-con is indicated for the prevention and treatment of nausea and vomiting associated with anesthesia and surgery.

Since the incidence of postoperative and postanesthetic vomiting has decreased with the adoption of modern techniques and agents, the prophylactic use of Emete-con should be restricted to those patients in whom emesis would endanger the results of surgery or result in harm to the patient.

CONTRAINDICATIONS

Emete-con is contraindicated in individuals who have demonstrated hypersensitivity to the drug.

WARNINGS

Use in Pregnancy

No teratogenic effects of benzquinamide were demonstrated in reproduction studies in chick embryos, mice, rats and rabbits. The relevance of these data to the human is not known. However, safe use of this drug in pregnancy has not been established and its use in pregnancy is not recommended.

Use in Children

As the data available at present are insufficient to establish proper dosage in children, the use of Emete-con in children is not recommended.

Intravenous Use

Sudden increase in blood pressure and transient arrhythmias (premature ventricular and auricular contractions) have been reported following intravenous administration of benzquinamide. Until a more predictable pattern of the effect of intravenous benzquinamide has been established, the intramuscular route of administration is considered preferable. The intravenous route of administration should be restricted to patients without cardiovascular disease and receiving no preanesthetic and/or concomitant cardiovascular drugs.

If patients receiving pressor agents or epinephrine-like drugs are also given benzquinamide, the latter should be given in fractions of the normal dose. Blood pressure should be monitored. Safeguards against hypertensive reactions are particularly important in hypertensive patients.

PRECAUTIONS

Benzquinamide, like other antiemetics, may mask signs of overdosage of toxic drugs or may obscure diagnosis of such conditions as intestinal obstruction and brain tumor.

ADVERSE REACTIONS

The following adverse reactions have been reported in subjects who have received benzquinamide. However, drowsiness appears to be the most common reaction. One case of pronounced allergic reaction has been encountered, characterized by pyrexia and urticaria.

System Affected

Autonomic Nervous System: Dry mouth, shivering, sweating, hiccoughs, flushing, salivation, blurred vision.

Continued on next page

Pfizer Inc—Cont.

Cardiovascular System: Hypertension, hypotension, dizziness, atrial fibrillation, premature auricular and ventricular contractions.
Hypertensive episodes have occurred after IM and IV administration.
Central Nervous System: Drowsiness, insomnia, restlessness, headache, excitement, nervousness.
Gastrointestinal System: Anorexia, nausea.
Musculoskeletal System: Twitching, shaking/tremors, weakness.
Skin: Hives/rash.
Other Systems: Fatigue, shaking chills, increased temperature.

DOSAGE AND ADMINISTRATION

Intramuscular: 50 mg (0.5 mg/kg–1.0 mg/kg)
First dose may be repeated in one hour with subsequent doses every 3-4 hours, as necessary. The precautions applicable to all intramuscular injections should be observed. Emete-con (benzquinamide hydrochloride) should be injected well within the mass of a larger muscle. The deltoid area should be used only if well developed. Injections should not be made into the lower and mid-thirds of the upper arm. Aspiration of the syringe should be carried out to avoid inadvertent intravascular injection.
Therapeutic blood levels and demonstrable antiemetic activity appear within fifteen minutes of intramuscular administration. When the objective of therapy is the prevention of nausea and vomiting, intramuscular administration is recommended at least fifteen minutes prior to emergence from anesthesia.
Intravenous: 25 mg (0.2 mg/kg–0.4 mg/kg as a single dose) administered slowly (1 ml per 0.5 to 1 minute). Subsequent doses should be given intramuscularly.
The intravenous route of administration should be restricted to patients without cardiovascular disease (See WARNINGS). If it is necessary to use Emete-con intravenously in elderly or debilitated patients, benzquinamide should be administered cautiously and the lower dose range is recommended.
This preparation must be initially reconstituted with 2.2 ml of Sterile Water for Injection, Bacteriostatic Water for Injection with benzyl alcohol or with methylparaben and propylparaben. This procedure yields 2 ml of a solution equivalent to 25 mg benzquinamide/ml, which maintains its potency for 14 days at room temperature.

OVERDOSAGE

Manifestations: On the basis of acute animal toxicology studies, gross Emete-con overdosage in humans might be expected to manifest itself as a combination of Central Nervous System stimulant and depressant effects. This speculation is derived from experimental studies in which intravenous doses of benzquinamide, at least 150 times the human therapeutic dose, were administered to dogs.
Treatment: There is no specific antidote for Emete-con overdosage. General supportive measures should be instituted, as indicated. Atropine may be helpful. Although there has been no direct experience with dialysis, it is not likely to be of value, since benzquinamide is extensively bound to plasma protein.

HOW SUPPLIED

Emete-con for IM/IV use is available in a vial containing benzquinamide HCl equivalent to 50 mg of benzquinamide in packages of 10 vials.

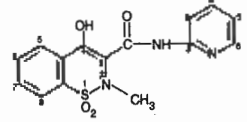
CAUTION

Federal law prohibits dispensing without prescription.
May 1977 60-1787-00-4

FELDENE® Rx
[fĕl'deen]
(piroxicam)
CAPSULES
For Oral Use

DESCRIPTION

FELDENE (piroxicam) is 4-Hydroxy-2-methyl-*N*-2-pyridinyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, an oxicam. Members of the oxicam family are not carboxylic acids, but they are acidic by virtue of the enolic 4-hydroxy substituent. FELDENE occurs as a white crystalline solid, sparingly soluble in water, dilute acid and most organic solvents. It is slightly soluble in alcohols and in aqueous alkaline solution. It exhibits a weakly acidic 4-hydroxy proton (pKa 5.1) and a weakly basic pyridyl nitrogen (pKa 1.8). It has the following structure:
[See chemical structure at top of next column.]



Molecular Formula: $C_{15}H_{13}N_3O_4S$
Molecular Weight 331.35

Inert ingredients in the formulations are: hard gelatin capsules (which may contain Blue 1, Red 3, and other inert ingredients); lactose; magnesium stearate; sodium lauryl sulfate; starch.

CLINICAL PHARMACOLOGY

FELDENE has shown anti-inflammatory, analgesic and antipyretic properties in animals. Edema, erythema, tissue proliferation, fever, and pain can all be inhibited in laboratory animals by the administration of FELDENE. It is effective regardless of the etiology of the inflammation. The mode of action of FELDENE is not fully established at this time. However, a common mechanism for the above effects may exist in the ability of FELDENE to inhibit the biosynthesis of prostaglandins, known mediators of inflammation.
It is established that FELDENE does not act by stimulating the pituitary-adrenal axis.
FELDENE is well absorbed following oral administration. Drug plasma concentrations are proportional for 10 and 20 mg doses, generally peak within three to five hours after medication, and subsequently decline with a mean half-life of 50 hours (range of 30 to 86 hours, although values outside of this range have been encountered).
This prolonged half-life results in the maintenance of relatively stable plasma concentrations throughout the day on once daily doses and to significant drug accumulation upon multiple dosing. A single 20 mg dose generally produces peak piroxicam plasma levels of 1.5 to 2 mcg/mL, while maximum drug plasma concentrations, after repeated daily ingestion of 20 mg FELDENE, usually stabilize at 3–8 mcg/mL. Most patients approximate steady state plasma levels within 7 to 12 days. Higher levels, which approximate steady state at two to three weeks, have been observed in patients in whom longer plasma half-lives of piroxicam occurred.
FELDENE and its biotransformation products are excreted in urine and feces, with about twice as much appearing in the urine as the feces. Metabolism occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugation of this product; by cyclodehydration; and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction, and N-demethylation. Less than 5% of the daily dose is excreted unchanged.
Concurrent administration of aspirin (3900 mg/day) and FELDENE (20 mg/day), resulted in a reduction of plasma levels of piroxicam to about 80% of their normal values. The use of FELDENE in conjunction with aspirin is not recommended because data are inadequate to demonstrate that the combination produces greater improvement than that achieved with aspirin alone and the potential for adverse reactions is increased. Concomitant administration of antacids had no effect on FELDENE plasma levels. The effects of impaired renal function or hepatic disease on plasma levels have not been established.
FELDENE, like salicylates and other nonsteroidal anti-inflammatory agents, is associated with symptoms of gastrointestinal tract irritation (see ADVERSE REACTIONS). However, in a study utilizing ^{51}Cr-tagged red blood cells, 20 mg of FELDENE administered as a single dose for four days did not result in a significant increase in fecal blood loss and did not detectably affect the gastric mucosa. In the same study a total daily dose of 3900 mg of aspirin, i.e., 972 mg q.i.d., caused a significant increase in fecal blood loss and mucosal lesions as demonstrated by gastroscopy.
In controlled clinical trials, the effectiveness of FELDENE (piroxicam) has been established for both acute exacerbations and long-term management of rheumatoid arthritis and osteoarthritis.
The therapeutic effects of FELDENE are evident early in the treatment of both diseases with a progressive increase in response over several (8–12) weeks. Efficacy is seen in terms of pain relief and, when present, subsidence of inflammation. Doses of 20 mg/day FELDENE display a therapeutic effect comparable to therapeutic doses of aspirin, with a lower incidence of minor gastrointestinal effects and tinnitus.
FELDENE has been administered concomitantly with fixed doses of gold and corticosteroids. The existence of a "steroid-sparing" effect has not been adequately studied to date.

INDICATIONS AND USAGE

FELDENE is indicated for acute or long-term use in the relief of signs and symptoms of the following:
1. osteoarthritis
2. rheumatoid arthritis
Dosage recommendations for use in children have not been established.

CONTRAINDICATIONS

FELDENE should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps, and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS

Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3–6 months, and in about 2–4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.
Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of piroxicam to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally, nephrotic syndrome.
A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.
Because of extensive renal excretion of piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged, see CLINICAL PHARMACOLOGY), lower doses of piroxicam should be anticipated in patients with impaired renal function, and they should be carefully monitored.
Although other nonsteroidal anti-inflammatory drugs do not have the same direct effects on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when FELDENE is administered.
Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.
As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

MARAX®

[mə'rax]

(ephedrine sulfate, theophylline, hydroxyzine HCl)
TABLETS AND DF SYRUP

CONTENTS

	Each Tablet Contains:	Each Teaspoon (5 ml) Syrup Contains:
Ephedrine Sulfate	25 mg	6.25 mg
Theophylline	130 mg	32.50 mg
Atarax® (hydroxyzine HCl)	10 mg	2.5 mg
Alcohol (Ethyl Alcohol)		5% v/v.

Inert ingredients for tablets are: alginic acid; magnesium stearate; precipitated calcium carbonate; sodium lauryl sulfate.

Inert ingredients for syrup are: alcohol; cherry flavor; hydrochloric acid; sodium benzoate; special flavor compound; sucrose; water.

ACTIONS

The action of ephedrine as a vasoconstrictor is well known. It is therefore of significant benefit in symptomatic relief of the congestion occurring in bronchial asthma. As a bronchodilator, it has a slower onset but longer duration of action than does epinephrine, which, in contrast to ephedrine, is not effective upon oral administration.

The diverse actions of theophylline—bronchospasmolytic, cardiovascular, and diuretic—are well established, and make it a particularly useful drug in the treatment of bronchial asthma, both in the acute attack and in the prophylactic therapy of the disease.

Atarax (hydroxyzine HCl) modifies the central stimulatory action of ephedrine preventing excessive excitation in patients on Marax therapy.

In animal studies Atarax has demonstrated antiserotonin activity and antispasmodic potency of a nonspecific nature.

Marax-DF Syrup produces an expectorant action wherein the tenacity of the sputum is decreased and the ease of expectoration is increased.

INDICATIONS

Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" Effective: For controlling bronchospastic disorders.

Final classification of the less than effective indication requires further investigation.

CONTRAINDICATIONS

Because of the ephedrine, Marax is contraindicated in cardiovascular disease, hyperthyroidism, and hypertension. This drug is contraindicated in individuals who have shown hypersensitivity to the drug or its components.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate to establish safety in early pregnancy. Until such data are available, hydroxyzine is contraindicated in early pregnancy.

PRECAUTIONS

Because of the ephedrine component this drug should be used with caution in elderly males or those with known prostatic hypertrophy.

The potentiating action of hydroxyzine, although mild, must be taken into consideration when the drug is used in conjunction with central nervous system depressants; and when other central nervous system depressants are administered concomitantly with hydroxyzine their dosage should be reduced. Patients should be cautioned that hydroxyzine can increase the effect of alcohol.

Patients should be warned—because of the hydroxyzine component—of the possibility of drowsiness occurring and cautioned against driving a car or operating dangerous machinery while taking this drug.

ADVERSE REACTIONS

With large doses of ephedrine, excitation, tremulousness, insomnia, nervousness, palpitation, tachycardia, precordial pain, cardiac arrhythmias, vertigo, dryness of the nose and throat, headache, sweating, and warmth may occur. Because ephedrine is a sympathomimetic agent some patients may develop vesical sphincter spasm and resultant urinary hesitation, and occasionally acute urinary retention. This should be borne in mind when administering preparations containing ephedrine to elderly males or those with known prostatic hypertrophy. At the recommended dose for Marax, a side effect occasionally reported is palpitation, and this can be controlled with dosage adjustment, additional amounts of concurrently administered Atarax (hydroxyzine HCl), or discontinuation of the medication. When ephedrine is given three or more times daily patients may develop tolerance after several weeks of therapy.

Theophylline when given on an empty stomach frequently causes gastric irritation accompanied by upper abdominal discomfort, nausea, and vomiting. Administration of the medication after meals will serve to minimize this side effect. Theophylline may cause diuresis and cardiac stimulation.

The amount of Atarax present in Marax has not resulted in disturbing side effects. When used alone specifically as a tranquilizer in the normal dosage range (25 to 50 mg three or four times a day), side effects are infrequent; even at these higher doses, no serious side effects have been reported and confirmed to date. Those which do occasionally occur when Atarax is used alone are drowsiness, xerostomia and, at extremely high doses, involuntary motor activity, unsteadiness of gait, neuromuscular weakness, all of which may be controlled by reduction of the dosage or discontinuation of the medication.

With the relatively low dose of Atarax in Marax, these effects are not likely to occur. In addition, the ataractic action of Atarax may modify the cardiac stimulatory action of ephedrine, and concurrently, increasing the amount of Atarax may control or abolish this undesirable effect of ephedrine.

DOSAGE AND ADMINISTRATION

The dosage of Marax should be adjusted according to the severity of complaints, and the patient's individual toleration.

Tablets: In general, an adult dose of 1 tablet, 2 to 4 times daily, should be sufficient. Some patients are controlled adequately with $^1/_2$ to 1 tablet at bedtime. The time interval between doses should not be shorter than four hours. The dosage for children over 5 years of age and for adults who are sensitive to ephedrine, is one-half the usual adult dose. Clinical experience to date has been confined to ages above 5 years.

Syrup: The dose for children over 5 years of age is 1 teaspoon (5 ml), 3 to 4 times daily. Dosage for children 2 to 5 years of age is $^1/_2$ to 1 teaspoon (2.5-5 ml), 3 to 4 times daily. Not recommended for children under 2 years of age.

HOW SUPPLIED

Marax Tablets are available as scored, dye free, m-shaped tablets in bottles of 100 (NDC 0049-2540-66) and 500 (NDC 0049-2540-73).

Marax-DF Syrup is available in pints (NDC 0049-2550-93) and gallons (NDC 0049-2550-54) as a colorless syrup, free of all coal tar dyes, and should be dispensed in tight, light-resistant containers (USP).

69-0928-32-7
66-2265-00-4

Shown in Product Identification Guide, page 328

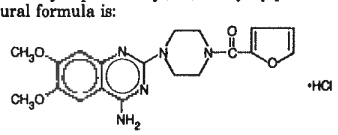
MINIPRESS® CAPSULES

[mĭn 'ĕ-prĕs]

(prazosin hydrochloride)
For Oral Use

DESCRIPTION

MINIPRESS® (prazosin hydrochloride), a quinazoline derivative, is the first of a new chemical class of antihypertensives. It is the hydrochloride salt of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl) piperazine and its structural formula is:



Molecular formula $C_{19}H_{21}N_5O_4 \cdot HCl$

It is a white, crystalline substance, slightly soluble in water and isotonic saline, and has a molecular weight of 419.87. Each 1 mg capsule of MINIPRESS for oral use contains drug equivalent to 1 mg free base.

Inert ingredients in the formulations are: hard gelatin capsules (which may contain Blue 1, Red 3, Red 28, Red 40, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; starch; sucrose.

CLINICAL PHARMACOLOGY

The exact mechanism of the hypotensive action of prazosin is unknown. Prazosin causes a decrease in total peripheral resistance and was originally thought to have a direct relaxant action on vascular smooth muscle. Recent animal studies, however, have suggested that the vasodilator effect of prazosin is also related to blockade of postsynaptic *alpha*-adrenoceptors. The results of dog forelimb experiments demonstrate that the peripheral vasodilator effect of prazosin is confined mainly to the level of the resistance vessels (arterioles). Unlike conventional *alpha*-blockers, the antihypertensive action of prazosin is usually not accompanied by a reflex tachycardia. Tolerance has not been observed to develop in long term therapy.

Hemodynamic studies have been carried out in man following acute single dose administration and during the course of long term maintenance therapy. The results confirm that the therapeutic effect is a fall in blood pressure unaccompanied by a clinically significant change in cardiac output, heart rate, renal blood flow and glomerular filtration rate. There is no measurable negative chronotropic effect.

In clinical studies to date, MINIPRESS (prazosin hydrochloride) has not increased plasma renin activity.

In man, blood pressure is lowered in both the supine and standing positions. This effect is most pronounced on the diastolic blood pressure.

Following oral administration, human plasma concentrations reach a peak at about three hours with a plasma half-life of two to three hours. The drug is highly bound to plasma protein. Bioavailability studies have demonstrated that the total absorption relative to the drug in a 20% alcoholic solution is 90%, resulting in peak levels approximately 65% of that of the drug in solution. Animal studies indicate that MINIPRESS (prazosin hydrochloride) is extensively metabolized, primarily by demethylation and conjugation, and excreted mainly via bile and feces. Less extensive human studies suggest similar metabolism and excretion in man.

In clinical studies in which lipid profiles were followed, there were generally no adverse changes noted between pre- and post-treatment lipid levels.

INDICATIONS AND USAGE

MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. It can be used alone or in combination with other antihypertensive drugs such as diuretics or beta-adrenergic blocking agents.

CONTRAINDICATIONS

None known.

WARNINGS

MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120–160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

PRECAUTIONS

Information for Patients: Dizziness or drowsiness may occur after the first dose of this medicine. Avoid driving or performing hazardous tasks for the first 24 hours after taking this medicine or when the dose is increased. Dizziness, lightheadedness or fainting may occur, especially when rising from a lying or sitting position. Getting up slowly may help lessen the problem. These effects may also occur if you drink alcohol, stand for long periods of time, exercise, or if the weather is hot. While taking MINIPRESS, be careful in the amount of alcohol you drink. Also, use extra care during exercise or hot weather, or if standing for long periods. Check with your physician if you have any questions.

Continued on next page

reactions have been caused by both the oral and parenteral administration of tetracyclines.
Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See "Warnings").
Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See "Warnings").
Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, and exacerbation of systemic lupus erythematosus.
Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages. These conditions disappeared rapidly when the drug was discontinued.
Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.
When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

DOSAGE AND ADMINISTRATION

Intramuscular Administration:
Adults: The usual daily dose is 250 mg administered once every 24 hours or 300 mg given in divided doses at 8 to 12 hour intervals.
For children above eight years of age: 15–25 mg/kg body weight up to a maximum of 250 mg per single daily injection. Dosage may be divided and given at 8 to 12 hour intervals.
Intramuscular therapy should be reserved for situations in which oral therapy is not feasible.
The intramuscular administration of oxytetracycline produces lower blood levels than oral administration in the recommended dosages. Patients placed on intramuscular oxytetracycline should be changed to the oral dosage form as soon as possible. If rapid, high blood levels are needed, oxytetracycline should be administered intravenously.
In patients with renal impairment: (See "Warnings") Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

HOW SUPPLIED

Terramycin (oxytetracycline) Intramuscular Solution is available as follows:
50 mg/mL—in 10 ml multiple dose vials, packages of 5 (NDC 0049-0750-77).

*U.S. Pat. Nos. 3,017,323 and 3,026,248
Revised March 1987 70-1051-00-2

TERRAMYCIN®

(oxytetracycline HCl with polymyxin B sulfate)
OPHTHALMIC OINTMENT
STERILE

DESCRIPTION

Each gram of sterile ointment contains oxytetracycline HCl equivalent to 5 mg oxytetracycline, 10,000 units of polymyxin B sulfate, white petrolatum, and liquid petrolatum.

ACTIONS

Terramycin® is a widely used antibiotic with clinically proved activity against gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain protozoa.
Polymyxin B Sulfate, one of a group of related antibiotics derived from *Bacillus polymyxa*, is rapidly bactericidal. This action is exclusively against gram-negative organisms. It is particularly effective against *Pseudomonas aeruginosa (B. pyocyaneus)* and Koch-Weeks bacillus, frequently found in local infections of the eye.
There is thus made available a particularly effective antimicrobial combination of the broad-spectrum antibiotic Terramycin as well as polymyxin B sulfate against primarily causative or secondarily infecting organisms.

INDICATIONS

The sterile preparation, Terramycin with Polymyxin B Sulfate Ophthalmic Ointment, is indicated for the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Terramycin with Polymyxin B Sulfate-susceptible organisms.
It may be administered topically alone, or as an adjunct to systemic therapy.
It is effective in infections caused by susceptible strains of staphylococci, streptococci, pneumococci, *Hemophilus influenzae, Pseudomonas aeruginosa*, Koch-Weeks bacillus, and *Proteus*.

CONTRAINDICATIONS

This drug is contraindicated in individuals who have shown hypersensitivity to any of its components.

PRECAUTIONS

As with all antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate specific therapy should be instituted.

ADVERSE REACTIONS

Terramycin with Polymyxin B Sulfate Ophthalmic Ointment is well tolerated by the epithelial membranes and other tissues of the eye. Allergic or inflammatory reactions due to individual hypersensitivity are rare.

DOSAGE AND ADMINISTRATION

Approximately $^1/_2$ inch of the ointment is squeezed from the tube onto the lower lid of the affected eye two to four times daily.
The patient should be instructed to avoid contamination of the tip of the tube when applying the ointment.

HOW SUPPLIED

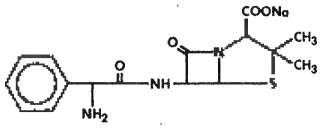
Terramycin with Polymyxin B Sulfate Ophthalmic Ointment is supplied in $^1/_8$ oz (3.5 g) tubes (NDC 0049-0801-08).
August 1987 60-2324-00-1

UNASYN®

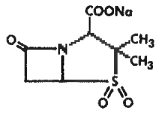
(ampicillin sodium/sulbactam sodium)

DESCRIPTION

UNASYN is an injectable antibacterial combination consisting of the semisynthetic antibiotic ampicillin sodium and the beta-lactamase inhibitor sulbactam sodium for intravenous and intramuscular administration.
Ampicillin sodium is derived from the penicillin nucleus, 6-aminopenicillanic acid. Chemically, it is monosodium (2S, 5R, 6R)-6-[(R)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate and has a molecular weight of 371.39. Its chemical formula is $C_{16}H_{18}N_3NaO_4S$. The structural formula is:



Sulbactam sodium is a derivative of the basic penicillin nucleus. Chemically, sulbactam sodium is sodium penicillinate sulfone; sodium (2S, 5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide. Its chemical formula is $C_8H_{10}NNaO_5S$ with a molecular weight of 255.22. The structural formula is:



UNASYN, ampicillin sodium/sulbactam sodium parenteral combination, is available as a white to off-white dry powder for reconstitution. UNASYN dry powder is freely soluble in aqueous diluents to yield pale yellow to yellow solutions containing ampicillin sodium and sulbactam sodium equivalent to 250 mg ampicillin per mL and 125 mg sulbactam per mL. The pH of the solutions is between 8.0 and 10.0.
Dilute solutions (up to 30 mg ampicillin and 15 mg sulbactam per mL) are essentially colorless to pale yellow. The pH of dilute solutions remains the same.
1.5 g of UNASYN (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt) parenteral contains approximately 115 mg (5 mEq) of sodium.
3 g of UNASYN (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt) parenteral contains approximately 230 mg (10 mEq) of sodium.

CLINICAL PHARMACOLOGY

General: Immediately after completion of a 15-minute intravenous infusion of UNASYN, peak serum concentrations of ampicillin and sulbactam are attained. Ampicillin serum levels are similar to those produced by the administration of equivalent amounts of ampicillin alone. Peak ampicillin serum levels ranging from 109 to 150 mcg/mL are attained after administration of 2000 mg of ampicillin plus 1000 mg sulbactam and 40 to 71 mcg/mL after administration of 1000 mg ampicillin plus 500 mg sulbactam. The corresponding mean peak serum levels for sulbactam range from 48 to 88 mcg/mL and 21 to 40 mcg/mL, respectively. After an intramuscular injection of 1000 mg ampicillin plus 500 mg sulbactam, peak ampicillin serum levels ranging from 8 to 37 mcg/mL and peak sulbactam serum levels ranging from 6 to 24 mcg/mL are attained.
The mean serum half-life of both drugs is approximately 1 hour in healthy volunteers.
Approximately 75 to 85% of both ampicillin and sulbactam are excreted unchanged in the urine during the first 8 hours after administration of UNASYN to individuals with normal renal function. Somewhat higher and more prolonged serum levels of ampicillin and sulbactam can be achieved with the concurrent administration of probenecid.
In patients with impaired renal function the elimination kinetics of ampicillin and sulbactam are similarly affected, hence the ratio of one to the other will remain constant whatever the renal function. The dose of UNASYN in such patients should be administered less frequently in accordance with the usual practice for ampicillin (see Dosage and Administration).
Ampicillin has been found to be approximately 28% reversibly bound to human serum protein and sulbactam approximately 38% reversibly bound.
The following average levels of ampicillin and sulbactam were measured in the tissues and fluids listed:

TABLE A
Concentration of UNASYN in Various Body Tissues and Fluids

Fluid or Tissue	Dose (grams) Ampicillin/ Sulbactam	Concentration (mcg/mL or mcg/g) Ampicillin/ Sulbactam
Peritoneal Fluid	0.5/0.5 IV	7/14
Blister Fluid (Cantharides)	0.5/0.5 IV	8/20
Tissue Fluid	1/0.5 IV	8/4
Intestinal Mucosa	0.5/0.5 IV	11/18
Appendix	2/1 IV	3/40

Penetration of both ampicillin and sulbactam into cerebrospinal fluid in the presence of inflamed meninges has been demonstrated after IV administration of UNASYN.

MICROBIOLOGY

Ampicillin is similar to benzyl penicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of cell wall mucopeptide biosynthesis. Ampicillin has a broad spectrum of bactericidal activity against many gram-positive and gram-negative aerobic and anaerobic bacteria. (Ampicillin is, however, degraded by beta-lactamases and therefore the spectrum of activity does not normally include organisms which produce these enzymes.)
A wide range of beta-lactamases found in microorganisms resistant to penicillins and cephalosporins have been shown in biochemical studies with cell free bacterial systems to be irreversibly inhibited by sulbactam. Although sulbactam alone possesses little useful antibacterial activity except against the *Neisseriacae*, whole organism studies have shown that sulbactam restores ampicillin activity against beta-lactamase producing strains. In particular, sulbactam has good inhibitory activity against the clinically important plasmid mediated beta-lactamases most frequently responsible for transferred drug resistance. Sulbactam has no effect on the activity of ampicillin against ampicillin susceptible strains.
The presence of sulbactam in the UNASYN formulation effectively extends the antibiotic spectrum of ampicillin to include many bacteria normally resistant to it and to other beta-lactam antibiotics. Thus, UNASYN possesses the properties of a broad-spectrum antibiotic and a beta-lactamase inhibitor.
While *in vitro* studies have demonstrated the susceptibility of most strains of the following organisms, clinical efficacy for infections other than those included in the indications section has not been documented.
Gram-Positive Bacteria: *Staphylococcus aureus* (beta-lactamase and non-beta-lactamase producing), *Staphylococcus epidermidis* (beta-lactamase and non-beta-lactamase producing), *Staphylococcus saprophyticus* (beta-lactamase and non-beta-lactamase producing), *Streptococcus faecalis*† (Enterococcus), *Streptococcus pneumoniae*† (formerly *D. pneumoniae*), *Streptococcus pyogenes*†, *Streptococcus viridans*†.
Gram-Negative Bacteria: *Hemophilus influenzae* (beta-lactamase and non-beta-lactamase producing). *Moraxella (Branhamella) catarrhalis* (beta-lactamase and non-beta-lactamase producing). *Escherichia coli* (beta-lactamase and non-beta-lactamase producing). *Klebsiella* species (all known strains are beta-lactamase producing). *Proteus mirabilis* (beta-lactamase and non-beta-lactamase producing). *Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Morganella morganii*, and *Neisseria gonorrhoeae* (beta-lactamase and non-beta-lactamase producing).
Anaerobes: *Clostridium* species†, *Peptococcus* species†, *Peptostreptococcus* species, *Bacteroides* species, including *B. fragilis*.
†These are not beta-lactamase producing strains and, therefore, are susceptible to ampicillin alone.

Continued on next page

Pfizer Inc—Cont.

Susceptibility Testing

Diffusion Technique: For the Kirby-Bauer method of susceptibility testing, a 20 mcg (10 mcg ampicillin + 10 mcg sulbactam) diffusion disk should be used. The method is one outlined in the NCCLS publication M2-A4.[1] With this procedure, a report from the laboratory of "Susceptible" indicates that the infecting organism is likely to respond to UNASYN therapy and a report of "Resistant" indicates that the infecting organism is not likely to respond to therapy. An "Intermediate" susceptibility report suggests that the infecting organism would be susceptible to UNASYN if a higher dosage is used or if the infection is confined to tissues or fluids (e.g., urine) in which high antibiotic levels are attained.

Dilution Techniques: Broth or agar dilution methods may be used to determine the minimal inhibitory concentration (MIC) value for susceptibility of bacterial isolates to ampicillin/sulbactam. The method used is one outlined in the NCCLS publication M7-A2.[2] Tubes should be inoculated to contain 10^5 to 10^6 organisms/mL or plates "spotted" with 10^4 organisms.

The recommended dilution method employs a constant ampicillin/sulbactam ratio of 2:1 in all tubes with increasing concentrations of ampicillin. MIC's are reported in terms of ampicillin concentration in the presence of sulbactam at a constant 2 parts ampicillin to 1 part sulbactam.

[See table below.]

INDICATIONS AND USAGE

UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus, Escherichia coli,* Klebsiella* spp.* (including *K. pneumoniae*), Proteus mirabilis,* Bacteroides fragilis,* Enterobacter* spp.,* and *Acinetobacter calcoaceticus.**

Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli, Klebsiella* spp. (including *K. pneumoniae*), Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*

Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli,** and *Bacteroides* spp.* (including *B. fragilis**).

* Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While UNASYN is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify the organisms causing infection and to determine their susceptibility to UNASYN.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies, when there is reason to believe the infection may involve any of the beta-lactamase producing organisms listed above in the indicated organ systems. Once the results are known, therapy should be adjusted if appropriate.

CONTRAINDICATIONS

The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including UNASYN, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.

Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentration of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with UNASYN.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)

Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS

UNASYN is generally well tolerated. The following adverse reactions have been reported.

Local Adverse Reactions

Pain at IM injection site—16%
Pain at IV injection site—3%
Thrombophlebitis—3%

Systemic Adverse Reactions

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.

Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.

Blood Chemistry: Decreased serum albumin and total proteins.

Renal: Increased BUN and creatinine.

Urinalysis: Presence of RBC's and hyaline casts in urine.

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.

Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, and enterocolitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin. (See WARNINGS.)

Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Some individuals have developed positive direct Coombs Tests during treatment with UNASYN, as with other beta-lactam antibiotics.

OVERDOSAGE

Neurological adverse reactions, including convulsions, may occur with the attainment of high CSF levels of beta-lactams. Ampicillin may be removed from circulation by hemodialysis. The molecular weight, degree of protein binding and pharmacokinetics profile of sulbactam suggest that this compound may also be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

UNASYN may be administered by either the IV or the IM routes.

For IV administration, the dose can be given by slow intravenous injection over at least 10–15 minutes or can also be de-

Recommended ampicillin/sulbactam, Susceptibility Ranges[1,2,3]

	Resistant	Intermediate	Susceptible
Gram(−) and Staphylococcus			
Bauer/Kirby Zone Sizes	≤11 mm	12–13 mm	≥14 mm
MIC (mcg of ampicillin/mL)	≥32	16	≤ 8
Hemophilus influenzae			
Bauer/Kirby Zone Sizes	≤19	—	≥20
MIC (mcg of ampicillin/mL)	≥ 4	—	≤2

[1]The non-beta-lactamase producing organisms which are normally susceptible to ampicillin, such as *Streptococci*, will have similar zone sizes as for ampicillin disks.

[2]*Staphylococci* resistant to methicillin, oxacillin, or nafcillin must be considered resistant to UNASYN.

[3]The quality control cultures should have the following assigned daily ranges for ampicillin/sulbactam:

		Disks	Mode MIC (mcg/mL ampicillin/mcg/mL sulbactam)
E. coli	(ATCC 25922)	20–24 mm	2/1
S. aureus	(ATCC 25923)	29–37 mm	0.12/0.06
E. coli	(ATCC 35218)	13–19 mm	8/4

Diluent	Maximum Concentration (mg/mL) UNASYN (Ampicillin/Sulbactam)	Use Periods
Sterile Water for Injection	45 (30/15)	8 hrs @ 25°C
	45 (30/15)	48 hrs @ 4°C
	30 (20/10)	72 hrs @ 4°C
0.9% Sodium Chloride Injection	45 (30/15)	8 hrs @ 25°C
	45 (30/15)	48 hrs @ 4°C
	30 (20/10)	72 hrs @ 4°C
5% Dextrose Injection	30 (20/10)	2 hrs @ 25°C
	30 (20/10)	4 hrs @ 4°C
	3 (2/1)	4 hrs @ 25°C
Lactated Ringer's Injection	45 (30/15)	8 hrs @ 25°C
	45 (30/15)	24 hrs @ 4°C
M/6 Sodium Lactate Injection	45 (30/15)	8 hrs @ 25°C
	45 (30/15)	8 hrs @ 4°C
5% Dextrose in 0.45% Saline	3 (2/1)	4 hrs @ 25°C
	15 (10/5)	4 hrs @ 4°C
10% Invert Sugar	3 (2/1)	4 hrs @ 25°C
	30 (20/10)	3 hrs @ 4°C

livered, in greater dilutions with 50–100 mL of a compatible diluent as an intravenous infusion over 15–30 minutes.

UNASYN may be administered by deep intramuscular injection. (See Preparation for Intramuscular Injection.)

The recommended adult dosage of UNASYN is 1.5 g (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt) to 3 g (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt) every six hours. This 1.5 to 3 g range represents the total of ampicillin content plus the sulbactam content of UNASYN, and corresponds to a range of 1 g ampicillin/0.5 g sulbactam to 2 g ampicillin/1 g sulbactam. The total dose of sulbactam should not exceed 4 grams per day.

Impaired Renal Function

In patients with impairment of renal function the elimination kinetics of ampicillin and sulbactam are similarly affected, hence the ratio of one to the other will remain constant whatever the renal function. The dose of UNASYN in such patients should be administered less frequently in accordance with the usual practice for ampicillin and according to the following recommendations:

UNASYN Dosage Guide For Patients With Renal Impairment

Creatinine Clearance (mL/min/ 1.73m²)	Ampicillin/ Sulbactam Half-Life (Hours)	Recommended UNASYN Dosage
≥ 30	1	1.5–3.0 g q 6h–q 8h
15–29	5	1.5–3.0 g q 12h
5–14	9	1.5–3.0 g q 24h

When only serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Males} \quad \frac{\text{weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$$

$$\text{Females} \quad 0.85 \times \text{above value}$$

COMPATABILITY, RECONSTITUTION AND STABILITY

UNASYN sterile powder is to be stored at or below 30°C (86°F) prior to reconstitution.

When concomitant therapy with aminoglycosides is indicated, UNASYN and aminoglycosides should be reconstituted and administered separately, due to the *in vitro* inactivation of aminoglycosides by any of the aminopenicillins.

DIRECTIONS FOR USE

General Dissolution Procedures: UNASYN sterile powder for intravenous and intramuscular use may be reconstituted with any of the compatible diluents described in this insert. Solutions should be allowed to stand after dissolution to allow any foaming to dissipate in order to permit visual inspection for complete solubilization.

Preparation for Intravenous Use

1.5 g and 3.0 g Bottles: UNASYN sterile powder in piggyback units may be reconstituted directly to the desired concentrations using any of the following parenteral diluents. Reconstitution of UNASYN, at the specified concentrations, with these diluents provide stable solutions for the time periods indicated in the following table: (After the indicated time periods, any unused portions of solutions should be discarded.) [See table above.]

If piggyback bottles are unavailable, standard vials of UNASYN sterile powder may be used. Initially, the vials may be reconstituted with Sterile Water for Injection to yield solutions containing 375 mg UNASYN per mL (250 mg ampicillin/125 mg sulbactam per mL). An appropriate volume should then be immediately diluted with a suitable parenteral diluent to yield solutions containing 3 to 45 mg UNASYN per mL (2 to 30 mg ampicillin/1 to 15 mg sulbactam per mL).

1.5 g ADD-Vantage® Vials: UNASYN in the ADD-Vantage® system is intended as a single dose for intravenous administration after dilution with the ADD-Vantage® Flexible Diluent Container containing 50 mL, 100 mL or 250 mL of 0.9% Sodium Chloride Injection, USP.

3 g ADD-Vantage® Vials: UNASYN in the ADD-Vantage® system is intended as a single dose for intravenous administration after dilution with the ADD-Vantage® Flexible Diluent Container containing 100 mL or 250 mL of 0.9% Sodium Chloride Injection, USP.

UNASYN in the ADD-Vantage® system is to be reconstituted with 0.9% Sodium Chloride Injection, USP only. See INSTRUCTIONS FOR USE OF THE ADD-Vantage® VIAL. Reconstitution of UNASYN, at the specified concentration, with 0.9% Sodium Chloride Injection, USP provides stable solutions for the time period indicated below:

Diluent	Maximum Concentration (mg/mL) UNASYN (Ampicillin/Sulbactam)	Use Period
0.9% Sodium Chloride Injection	30 (20/10)	8 hrs @ 25°C

In 0.9% Sodium Chloride Injection, USP

The final diluted solution of UNASYN should be completely administered *within 8 hours* in order to assure proper potency.

Preparation for Intramuscular Injection

1.5 g and 3.0 g Standard Vials: Vials for intramuscular use may be reconstituted with Sterile Water for Injection USP, 0.5% Lidocaine Hydrochloride Injection USP or 2% Lidocaine Hydrochloride Injection USP. Consult the following table for recommended volumes to be added to obtain solutions containing 375 mg UNASYN per mL (250 mg ampicillin/125 mg sulbactam per mL). Note: *Use only freshly prepared solutions and administer within one hour after preparation.*

UNASYN Vial Size	Volume of Diluent to be Added	Withdrawal Volume*
1.5 g	3.2 mL	4.0 mL
3.0 g	6.4 mL	8.0 mL

*There is sufficient excess present to allow withdrawal and administration of the stated volumes.

Animal Pharmacology: While reversible glycogenosis was observed in laboratory animals, this phenomenon was dose- and time-dependent and is not expected to develop at the therapeutic doses and corresponding plasma levels attained during the relatively short periods of combined ampicillin/sulbactam therapy in man.

HOW SUPPLIED

UNASYN (ampicillin sodium/sulbactam sodium) is supplied as a sterile off-white dry powder in glass vials and piggyback bottles. The following packages are available:

Vials containing 1.5 g (NDC 0049-0013-83) equivalent of UNASYN (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt)

Vials containing 3 g (NDC 0049-0014-83) equivalent of UNASYN (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt)

Bottles containing 1.5 g (NDC 0049-0022-83) equivalent of UNASYN (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt)

Bottles containing 3 g (NDC 0049-0023-83) equivalent of UNASYN (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt)

Pharmacy Bulk Package containing 15 g (NDC 0049-0024-28) equivalent of UNASYN (10 g ampicillin as the sodium salt plus 5 g sulbactam as the sodium salt)

ADD-Vantage® vials containing 1.5 g (NDC 0049-0031-83) equivalent of UNASYN (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt) are distributed by Pfizer Inc.

ADD-Vantage® vials containing 3 g (NDC 0049-0032-83) equivalent of UNASYN (2 g ampicillin as the sodium salt plus 1 g sulbactum as the sodium salt) are distributed by Pfizer Inc.

The 1.5 g UNASYN ADD-Vantage® vials are only to be used with Abbott Laboratories' ADD-Vantage® Flexible Diluent Container containing 0.9% Sodium Chloride Injection, USP, 50 mL, 100 mL, or 250 mL sizes.

The 3 g UNASYN ADD-Vantage® vials are only to be used with Abbott Laboratories' ADD-Vantage® Flexible Diluent Container containing 0.9% Sodium Chloride Injection, USP, 100 mL or 250 mL sizes.

INSTRUCTIONS FOR USE OF THE ADD-Vantage® VIAL

To Open Diluent Container: Peel overwrap from the corner and remove container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container: (Use Aseptic Technique)

1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:

a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (see Figure 1), pull the ring approximately half way around the cap and then pull straight up to remove the cap (see Figure 2).

NOTE: Do not access vial with syringe.

Figure 1

Figure 2

b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (See Figure 3.)

2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately $^1/_2$ turn (180°) after the first audible click. (See Figure 4.) The clicking sound does not assure a seal, the vial must be turned as far as it will go.
   NOTE: Once vial is sealed, do not attempt to remove. (See Figure 4.)
3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.
4. Label appropriately.

Figure 3

Figure 4

To Prepare Admixture

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.
2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (See Figure 5.)
3. Pull the inner cap from the drug vial. (See Figure 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.
4. Mix container contents thoroughly and use within the specified time.

Figure 5

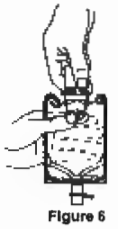


Figure 6

Continued on next page

Pfizer Inc—Cont.

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1. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests*—Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7 NCCLS. Villanova, PA. April 1990.
2. National Committee for Clinical Laboratory Standards, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*. Second Edition. Approved Standard NCCLS Document M7-A2. Vol. 10, No. 8 NCCLS. Villanova, PA. April 1990.

69-4361-00-2 Rev. Jan. 1994

Shown in Product Identification Guide, page 328

UROBIOTIC®-250 ℞

[*u "rō-bī-ot 'ik*]
CAPSULES

Each capsule contains
Oxytetracycline hydrochloride
equivalent to ..... 250 mg. oxytetracycline
Sulfamethizole ..... 250 mg
Phenazopyridine hydrochloride ..... 50 mg

Inert ingredients in the formulation are: hard gelatin capsules (which may contain Green 3, Yellow 6, Yellow 10 and other inert ingredients); magnesium stearate; sodium lauryl sulfate; starch.

ACTIONS

Urobiotic-250 is a product designed for use specifically in urinary tract infections.

Terramycin® (oxytetracycline HCl) is a widely used antibiotic with clinically proved activity against gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain protozoa. Terramycin is well tolerated and well absorbed after oral administration. It diffuses readily through the placenta and is present in the fetal circulation. It diffuses into the pleural fluid, and under some circumstances, into the cerebrospinal fluid. Oxytetracycline HCl appears to be concentrated in the hepatic system and is excreted in the bile. It is excreted in the urine and in the feces, in high concentrations, in a biologically active form.

Sulfamethizole is a chemotherapeutic agent active against a number of important gram-positive and gram-negative bacteria. This sulfonamide is well absorbed, has a low degree of acetylation, and is extremely soluble. Because of these features and its rapid renal excretion, sulfamethizole has a low order of toxicity and provides prompt and high concentrations of the active drug in the urinary tract.

Phenazopyridine is an orally absorbed agent which produces prompt and effective local analgesia and relief of urinary symptoms by virtue of its rapid excretion in the urinary tract. These effects are confined to the genitourinary system and are not accompanied by generalized sedation or narcosis.

INDICATIONS

Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

"Lacking substantial evidence of effectiveness as a fixed combination":

Urobiotic-250 is indicated in the therapy of a number of genitourinary infections caused by susceptible organisms. These infections include the following: pyelonephritis, pyelitis, ureteritis, cystitis, prostatitis, and urethritis.

Since both Terramycin and sulfamethizole provide effective levels in blood, tissue, and urine, Urobiotic-250 provides a multiple antimicrobial approach at the site of infection. Both antibacterial components are active against the most common urinary pathogens, including *Escherichia coli, Pseudomonas aeruginosa, Aerobacter aerogenes, Streptococcus faecalis, Streptococcus hemolyticus, and Micrococcus pyogenes.* Urobiotic-250 is particularly useful in the treatment of infections caused by bacteria more sensitive to the combination than to either component alone. The combination is also of value in those cases with mixed infections, and in those instances where the causative organism is unknown pending laboratory isolation.

Final classification of the less than effective indications requires further investigation. Clinical studies to substantiate the efficacy of Urobiotic-250 are ongoing. Completion of these ongoing studies will provide data for final classification of these indications.

CONTRAINDICATIONS

This drug is contraindicated in individuals who have shown hypersensitivity to any of its components.

This drug, because of the sulfonamide component, should not be used in patients with a history of sulfonamide sensitivities, and in pregnant females at term.

WARNINGS

If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity. Under such conditions, lower than usual doses are indicated and if therapy is prolonged, tetracycline serum level determinations may be advisable.

Oxytetracycline HCl, which is one of the ingredients of Urobiotic-250, may form a stable calcium complex in any bone-forming tissue with no serious harmful effects reported thus far in humans. However, use of oxytetracycline during tooth development (last trimester of pregnancy, neonatal period and early childhood) may cause discoloration of the teeth (yellow-grey-brownish). This effect occurs mostly during long term use of the drug but it also has been observed in usual short treatment courses.

Because of its sulfonamide content, this drug should be used only after critical appraisal in patients with liver damage, renal damage, urinary obstruction, or blood dyscrasias. Deaths have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, and other blood dyscrasias associated with sulfonamide administration. When used intermittently, or for a prolonged period, blood counts and liver and kidney function tests should be performed.

Certain hypersensitive individuals may develop a photodynamic reaction precipitated by exposure to direct sunlight during the use of this drug. This reaction is usually of the photoallergic type which may also be produced by other tetracycline derivatives. Individuals with a history of photosensitivity reactions should be instructed to avoid exposure to direct sunlight while under treatment with this or other tetracycline drugs, and treatment should be discontinued at first evidence of skin discomfort.

NOTE: Reactions of a photoallergic nature are exceedingly rare with Terramycin (oxytetracycline HCl). Phototoxic reactions are not believed to occur with Terramycin.

PRECAUTIONS

As with all antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate specific therapy should be instituted. This drug should be used with caution in persons having histories of significant allergies and/or asthma.

ADVERSE REACTIONS

Glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature, may occur during oxytetracycline HCl therapy, but are rare. If adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule forms of drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (See Dosage and Administration.)

With oxytetracycline therapy bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages. These conditions disappeared rapidly when the drug was discontinued.

As in all sulfonamide therapy, the following reactions may occur: nausea, vomiting, diarrhea, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, skin rash, infection of the conjunctiva and sclera, petechiae, purpura, hematuria and crystalluria. The dosage should be decreased or the drug withdrawn, depending upon the severity of the reaction.

DOSAGE AND ADMINISTRATION

Urobiotic-250 is recommended in adults only. A dose of 1 capsule four times daily is suggested. In refractory cases 2 capsules four times a day may be used.

Therapy should be continued for a minimum of seven days or until bacteriologic cure in acute urinary tract infections.

Administration of adequate amounts of fluid along with capsule forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. (See Adverse Reactions.)

To aid absorption of the drug, it should be given at least one hour before or two hours after eating. Aluminum hydroxide gel given with antibiotics has been shown to decrease their absorption and is contraindicated.

SUPPLY

Urobiotic-250 capsules: bottles of 50 (NDC 0049-0920-50), and unit dose packages of 100 (10 × 10's) (NDC 0049-0920-41).

LITERATURE AVAILABLE

Yes.

70-1636-00-9
Revised Dec. 1986

VIBRAMYCIN® Calcium ℞

[*vī-brə 'mīs-ᵊn*]
doxycycline calcium
oral suspension
SYRUP

VIBRAMYCIN® Hyclate

[*vī-brə 'mīs-ᵊn*]
doxycycline hyclate
CAPSULES

VIBRAMYCIN® Monohydrate

[*vī-brə 'mīs-ᵊn*]
doxycycline monohydrate
for ORAL SUSPENSION

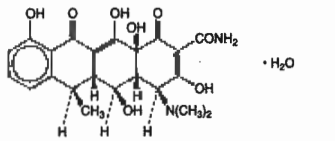
VIBRA-TABS®

[*vī-brə 'mīs-ᵊn*]
doxycycline hyclate
FILM COATED TABLETS

DESCRIPTION

Vibramycin is a broad-spectrum antibiotic synthetically derived from oxytetracycline, and is available as Vibramycin Monohydrate (doxycycline monohydrate); Vibramycin Hyclate and Vibra-Tabs (doxycycline hydrochloride hemiethanolate hemihydrate); and Vibramycin Calcium (doxycycline calcium) for oral administration.

The structural formula of doxycycline monohydrate is



with a molecular formula of $C_{22}H_{24}N_2O_8 \cdot H_2O$ and a molecular weight of 462.46. The chemical designation for doxycycline is 4-(Dimethylamino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 5, 10, 12, 12a-pentahydroxy-6-methyl-1, 11-dioxo-2-naphthacenecarboxamide monohydrate. The molecular formula for doxycycline hydrochloride hemiethanolate hemihydrate is $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$ and the molecular weight is 1025.89. Doxycycline is a light-yellow crystalline powder. Doxycycline hyclate is soluble in water, while doxycycline monohydrate is very slightly soluble in water.

Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Inert ingredients in the syrup formulation are: apple flavor; butylparaben; calcium chloride; carmine; glycerin; hydrochloric acid; magnesium aluminum silicate; povidone; propylene glycol; propylparaben; raspberry flavor; simethicone emulsion; sodium hydroxide; sodium metabisulfite; sorbitol solution; water.

Inert ingredients in the capsule formulations are: hard gelatin capsules (which may contain Blue 1 and other inert ingredients); magnesium stearate; microcrystalline cellulose; sodium lauryl sulfate.

Inert ingredients for the oral suspension formulation are: carboxymethylcellulose sodium; Blue 1; methylparaben; microcrystalline cellulose; propylparaben; raspberry flavor; Red 28; simethicone emulsion; sucrose.

Inert ingredients for the tablet formulation are: ethylcellulose; hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; propylene glycol; sodium lauryl sulfate; talc; titanium dioxide; Yellow 6 Lake.

CLINICAL PHARMACOLOGY

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile, and excreted in the urine and feces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral administration. Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 mcg/mL of doxycycline at 2 hours decreasing to 1.45 mcg/mL at 24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 mL/min.). This percentage excretion may fall as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min.). Studies have shown no significant difference in serum half-life of doxycycline (range 18–22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

Results of animal studies indicate that tetracyclines cross the placenta and are found in fetal tissues.

Microbiology

The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including doxycycline, have a similar antimicrobial spectrum of activity

Pfizer Inc—Cont.

mL) must be completed within six hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Solutions must be used within this time period or discarded.
Solutions of Vibramycin (doxycycline hyclate for injection) at a concentration of 10 mg/mL in Sterile Water for Injection, when frozen immediately after reconstitution are stable for 8 weeks when stored at −20°C. If the product is warmed, care should be taken to avoid heating it after the thawing is complete. Once thawed the solution should not be refrozen.

HOW SUPPLIED

Vibramycin (doxycycline hyclate for injection) Intravenous is available as a sterile powder in a vial containing doxycycline hyclate equivalent to 100 mg of doxycycline with 480 mg of ascorbic acid, packages of 5 (NDC 0049-0960-77).
65-1940-00-2

LITERATURE AVAILABLE

Yes.

VISTARIL® ℞

[vĭs 'tăr-ĭl]
(hydroxyzine pamoate)
Capsules and Oral Suspension

DESCRIPTION

Hydroxyzine pamoate is designated chemically as 1-(p-chlorobenzhydryl) 4-[2- (2-hydroxyethoxy) ethyl] diethylenediamine salt of 1,1'- methylene bis (2 hydroxy-3-naphthalene carboxylic acid).
Inert ingredients for the capsule formulations are: hard gelatin capsules (which may contain Yellow 10, Green 3, Yellow 6, Red 33, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; starch; sucrose.
Inert ingredients for the oral suspension formulation are: carboxymethylcellulose sodium; lemon flavor; propylene glycol; sorbic acid; sorbitol solution; water.

CLINICAL PHARMACOLOGY

Vistaril® (hydroxyzine pamoate) is unrelated chemically to the phenothiazines, reserpine, meprobamate, or the benzodiazepines.
Vistaril is not a cortical depressant, but its action may be due to a suppression of activity in certain key regions of the subcortical area of the central nervous system. Primary skeletal muscle relaxation has been demonstrated experimentally. Bronchodilator activity, and antihistaminic and analgesic effects have been demonstrated experimentally and confirmed clinically. An antiemetic effect, both by the apomorphine test and the veriloid test, has been demonstrated. Pharmacological and clinical studies indicate that hydroxyzine in therapeutic dosage does not increase gastric secretion or acidity and in most cases has mild antisecretory activity. Hydroxyzine is rapidly absorbed from the gastrointestinal tract and Vistaril's clinical effects are usually noted within 15 to 30 minutes after oral administration.

INDICATIONS

For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested.
Useful in the management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatoses, and in histamine-mediated pruritus.
As a sedative when used as premedication and following general anesthesia, **Hydroxyzine may potentiate meperidine (Demerol®) and barbiturates,** so their use in pre-anesthetic adjunctive therapy should be modified on an individual basis. Atropine and other belladonna alkaloids are not affected by the drug. Hydroxyzine is not known to interfere with the action of digitalis in any way and it may be used concurrently with this agent.
The effectiveness of hydroxyzine as an antianxiety agent for long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should reassess periodically the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat and mouse at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate to establish safety in early pregnancy. Until such data are available, hydroxyzine is contraindicated in early pregnancy.
Hydroxyzine pamoate is contraindicated for patients who have shown a previous hypersensitivity to it.

WARNINGS

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since many drugs are so excreted, hydroxyzine should not be given to nursing mothers.

PRECAUTIONS

THE POTENTIATING ACTION OF HYDROXYZINE MUST BE CONSIDERED WHEN THE DRUG IS USED IN CONJUNCTION WITH CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS, NON-NARCOTIC ANALGESICS AND BARBITURATES. Therefore, when central nervous system depressants are administered concomitantly with hydroxyzine, their dosage should be reduced. Since drowsiness may occur with use of the drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery while taking Vistaril (hydroxyzine pamoate). Patients should be advised against the simultaneous use of other CNS depressant drugs, and cautioned that the effect of alcohol may be increased.

ADVERSE REACTIONS

Side effects reported with the administration of Vistaril are usually mild and transitory in nature.
Anticholinergic: Dry mouth.
Central Nervous System: Drowsiness is usually transitory and may disappear in a few days of continued therapy or upon reduction of the dose. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended. Clinically significant respiratory depression has not been reported at recommended doses.

OVERDOSAGE

The most common manifestation of overdosage of Vistaril is hypersedation. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken.
If vomiting has not occurred spontaneously, it should be induced. Immediate gastric lavage is also recommended. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated. Hypotension, though unlikely, may be controlled with intravenous fluids and Levophed® (levarterenol) or Aramine® (metaraminol). Do not use epinephrine, as Vistaril counteracts its pressor action. Caffeine and Sodium Benzoate Injection, USP, may be used to counteract central nervous system depressant effects.
There is no specific antidote. It is doubtful that hemodialysis would be of any value in the treatment of overdosage with hydroxyzine. However, if other agents such as barbiturates have been ingested concomitantly, hemodialysis may be indicated. There is no practical method to quantitate hydroxyzine in body fluids or tissue after its ingestion or administration.

DOSAGE

For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested: in adults, 50–100 mg q.i.d.; children under 6 years, 50 mg daily in divided doses and over 6 years, 50–100 mg daily in divided doses.
For use in the management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatoses, and in histamine-mediated pruritus: in adults, 25 mg t.i.d. or q.i.d.; children under 6 years, 50 mg daily in divided doses and over 6 years, 50–100 mg daily in divided doses.
As a sedative when used as a premedication and following general anesthesia: 50–100 mg in adults, and 0.6 mg/kg in children.
When treatment is initiated by the intramuscular route of administration, subsequent doses may be administered orally.
As with all medications, the dosage should be adjusted according to the patient's response to therapy.

HOW SUPPLIED

Vistaril® Capsules (hydroxyzine pamoate equivalent to hydroxyzine hydrochloride)

25 mg:	100's (NDC 0069-5410-66), 500's (NDC 0069-5410-73), and Unit Dose (10 × 10's) (NDC 0069-5410-41) two-tone green capsules
50 mg:	100's (NDC 0069-5420-66), 500's (NDC 0069-5420-73), and Unit Dose (10 × 10's) (NDC 0069-5420-41) green and white capsules
100 mg:	100's (NDC 0069-5430-66), 500's (NDC 0069-5430-73), and Unit Dose (10 × 10's) (NDC 0069-5430-41) green and gray capsules

Vistaril® Oral Suspension (hydroxyzine pamoate equivalent to 25 mg hydroxyzine hydrochloride per teaspoonful-5 mL): 1 pint (473 mL) bottles (NDC 0069-5440-93) and 4 ounce (120 mL) bottles (NDC 0069-5440-97) in packages of 4.
Shake vigorously until product is completely resuspended.

BIBLIOGRAPHY

Available on request.
69-0846-00-1 Revised November 1994
Shown in Product Identification Guide, page 328

VISTARIL® ℞

hydroxyzine hydrochloride
Intramuscular Solution
For Intramuscular Use Only

CHEMISTRY

Hydroxyzine hydrochloride is designated chemically as 1-(p-chlorobenzhydryl) 4-[2-(2-hydroxyethoxy) ethyl] piperazine dihydrochloride.

ACTIONS

VISTARIL (hydroxyzine hydrochloride) is unrelated chemically to phenothiazine, reserpine, and meprobamate. Hydroxyzine has demonstrated its clinical effectiveness in the chemotherapeutic aspect of the total management of neuroses and emotional disturbances manifested by anxiety, tension, agitation, apprehension or confusion.
Hydroxyzine has been shown clinically to be a rapid-acting true ataraxic with a wide margin of safety. It induces a calming effect in anxious, tense, psychoneurotic adults and also in anxious, hyperkinetic children without impairing mental alertness. It is not a cortical depressant, but its action may be due to a suppression of activity in certain key regions of the subcortical area of the central nervous system.
Primary skeletal muscle relaxation has been demonstrated experimentally.
Hydroxyzine has been shown experimentally to have antispasmodic properties, apparently mediated through interference with the mechanism that responds to spasmogenic agents such as serotonin, acetylcholine, and histamine.
Antihistaminic effects have been demonstrated experimentally and confirmed clinically.
An antiemetic effect, both by the apomorphine test and the veriloid test, has been demonstrated. Pharmacological and clinical studies indicate that hydroxyzine in therapeutic dosage does not increase gastric secretion or acidity and in most cases provides mild antisecretory benefits.

INDICATIONS

The total management of anxiety, tension, and psychomotor agitation in conditions of emotional stress requires in most instances a combined approach of psychotherapy and chemotherapy. Hydroxyzine has been found to be particularly useful for this latter phase of therapy in its ability to render the disturbed patient more amenable to psychotherapy in long term treatment of the psychoneurotic and psychotic, although it should not be used as the sole treatment of psychosis or of clearly demonstrated cases of depression.
Hydroxyzine is also useful in alleviating the manifestations of anxiety and tension as in the preparation for dental procedures and in acute emotional problems. It has also been recommended for the management of anxiety associated with organic disturbances and as adjunctive therapy in alcoholism and allergic conditions with strong emotional overlay, such as in asthma, chronic urticaria, and pruritus.
VISTARIL (hydroxyzine hydrochloride) Intramuscular Solution is useful in treating the following types of patients when intramuscular administration is indicated:
1. The acutely disturbed or hysterical patient.
2. The acute or chronic alcoholic with anxiety withdrawal symptoms or delirium tremens.
3. As pre- and postoperative and pre- and postpartum adjunctive medication to permit reduction in narcotic dosage, allay anxiety and control emesis.

VISTARIL (hydroxyzine hydrochloride) has also demonstrated effectiveness in controlling nausea and vomiting, excluding nausea and vomiting of pregnancy. (See Contraindications.)
In prepartum states, the reduction in narcotic requirement effected by hydroxyzine is of particular benefit to both mother and neonate.
Hydroxyzine benefits the cardiac patient by its ability to allay the associated anxiety and apprehension attendant to certain types of heart disease. Hydroxyzine is not known to interfere with the action of digitalis in any way and may be used concurrently with this agent.
The effectiveness of hydroxyzine in long term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should reassess periodically the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Hydroxyzine hydrochloride intramuscular solution is intended only for intramuscular administration and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.
This drug is contraindicated for patients who have shown a previous hypersensitivity to it.
Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate to establish safety in early pregnancy. Until such data are available, hydroxyzine is contraindicated in early pregnancy.

PRECAUTIONS

THE POTENTIATING ACTION OF HYDROXYZINE MUST BE CONSIDERED WHEN THE DRUG IS USED IN CONJUNCTION WITH CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS, BARBITURATES, AND ALCOHOL. Rarely, cardiac arrests and death have been reported in association with the combined use of hydroxyzine hydrochloride IM and other CNS depressants. Therefore when central nervous system depressants are administered concomitantly with hydroxyzine their dosage should be reduced up to 50 per cent. The efficacy of hydroxyzine as adjunctive pre- and postoperative sedative medication has also been well established, especially as regards its ability to allay anxiety, control emesis, and reduce the amount of narcotic required.

HYDROXYZINE MAY POTENTIATE NARCOTICS AND BARBITURATES, so their use in preanesthetic adjunctive therapy should be modified on an individual basis. Atropine and other belladonna alkaloids are not affected by the drug.

When hydroxyzine is used preoperatively or prepartum, narcotic requirements may be reduced as much as 50 per cent. Thus, when 50 mg of VISTARIL (hydroxyzine hydrochloride) Intramuscular Solution is employed, meperidine dosage may be reduced from 100 mg to 50 mg. The administration of meperidine may result in severe hypotension in the postoperative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume. Meperidine should be used with great caution and in reduced dosage in patients who are receiving other pre- and/or postoperative medications and in whom there is a risk of respiratory depression, hypotension, and profound sedation or coma occurring. Before using any medications concomitant with hydroxyzine, the manufacturer's prescribing information should be read carefully.

Since drowsiness may occur with the use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery while taking this drug.

As with all intramuscular preparations, VISTARIL Intramuscular Solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage.

ADULTS: The preferred site is the upper outer quadrant of the buttock, (i.e., gluteus maximus), or the mid-lateral thigh.

CHILDREN: It is recommended that intramuscular injections be given preferably in the mid-lateral muscles of the thigh. In infants and small children the periphery of the upper outer quadrant of the gluteal region should be used only when necessary, such as in burn patients, in order to minimize the possibility of damage to the sciatic nerve.

The deltoid area should be used only if well developed such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-third of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

ADVERSE REACTIONS

Therapeutic doses of hydroxyzine seldom produce impairment of mental alertness. However, drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon reduction of the dose. Dryness of the mouth may be encountered at higher doses. Extensive clinical use has substantiated the absence of toxic effects on the liver or bone marrow when administered in the recommended doses for over four years of uninterrupted therapy. The absence of adverse effects has been further demonstrated in experimental studies in which excessively high doses were administered.

Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended. Continuous therapy with over one gram per day has been employed in some patients without these effects having been encountered.

DOSAGE AND ADMINISTRATION

The recommended dosages for VISTARIL (hydroxyzine hydrochloride) Intramuscular Solution are:

For adult psychiatric and emotional emergencies, including acute alcoholism.	IM: 50–100 mg stat., and q. 4–6h., p.r.n.
Nausea and vomiting excluding nausea and vomiting of pregnancy.	Adults: 25–100 mg IM Children: 0.5 mg/lb body weight IM
Pre- and postoperative adjunctive medication.	Adults: 25–100 mg IM Children: 0.5 mg/lb body weight IM
Pre- and postpartum adjunctive therapy.	25–100 mg IM

As with all potent medications, the dosage should be adjusted according to the patient's response to therapy.

FOR ADDITIONAL INFORMATION OF THE ADMINISTRATION AND SITE OF SELECTION SEE PRECAUTIONS SECTION. NOTE: VISTARIL (hydroxyzine hydrochloride) Intramuscular Solution may be administered without further dilution.

Patients may be started on intramuscular therapy when indicated. They should be maintained on oral therapy whenever this route is practicable.

HOW SUPPLIED

VISTARIL (hydroxyzine hydrochloride) Intramuscular Solution

Multi-Dose Vials

25 mg/mL: 10 mL vials (NDC 0049-5450-74)

50 mg/mL: 10 mL vials (NDC 0049-5460-74)

Unit Dose Vials

50 mg/mL–1 mL fill: packages of 25 vials (NDC 0049-5462-76)

100 mg/2 mL–2 mL fill: packages of 25 vials (NDC 0049-5460-76)

STORAGE

Store below 86° F (30°C).

Protect from freezing.

FORMULA

Dosage Strength	25 mg/1 mL	50 mg/1 mL 100 mg/2 mL
Hydroxyzine hydrochloride	25 mg/mL	50 mg/mL
Benzyl Alcohol	0.9%	0.9%
Sodium hydroxide	to adjust to optimum pH	

70-0843-00-5

Revised May 1993

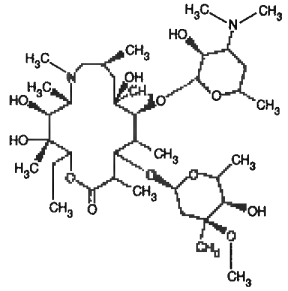
ZITHROMAX®

(azithromycin capsules)
and
(azithromycin for oral suspension)

℞

DESCRIPTION

ZITHROMAX® (azithromycin capsules and azithromycin for oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (*2R,3S,4R,5R,8R,10R,11R,12S,13S,14R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L-ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D-xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.00. Azithromycin has the following structural formula:



Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12} \cdot 2H_2O$ and a molecular weight of 785.0.

ZITHROMAX® capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard-gelatin capsules (containing FD&C Red #40). They also contain the following inactive ingredients: anhydrous lactose, corn starch, magnesium stearate, and sodium lauryl sulfate.

It is also supplied as a powder for oral suspension.

ZITHROMAX® for oral suspension is supplied in bottles containing 300 mg, 600 mg, 900 mg, or 1200 mg azithromycin dihydrate powder equivalent to 300 mg, 600 mg, 900 mg, 1200 mg azithromycin per bottle and the following inactive ingredients: sucrose; sodium phosphate, tribasic, anhydrous; hydroxypropyl cellulose; xanthan gum; FD&C Red #40; and spray dried artificial cherry, creme de vanilla, and banana flavors. After constitution, each 5 mL of suspension contains 100 mg or 200 mg of azithromycin.

CLINICAL PHARMACOLOGY

Adult Pharmacokinetics: Following oral administration, azithromycin is rapidly absorbed and widely distributed throughout the body. Rapid distribution of azithromycin into tissues and high concentration within cells result in significantly higher azithromycin concentrations in tissues than in plasma or serum.

The pharmacokinetic parameters of azithromycin capsules in plasma after dosing 500 mg loading dose on day 1 followed by 250 mg q.d. on days 2 through 5 in healthy young adults (age 18–40 years old) are portrayed in the following chart:

Pharmacokinetic Parameters (Mean)	Total n = 12 Day 1	Day 5
C_{max} (μg/mL)	0.41	0.24
T_{max} (h)	2.5	3.2
AUC_{0-24} (μg·h/mL)	2.6	2.1
C_{min} (μg/mL)	0.05	0.05
Urinary Excret. (% dose)	4.5	6.5

In this study, there was no significant difference in the disposition of azithromycin between male and female subjects. Plasma concentrations of azithromycin declined in a polyphasic pattern resulting in an average terminal half-life of 68 hours. With this regimen, C_{min} and C_{max} remained essentially unchanged from day 2 through day 5 of therapy. However, without a loading dose, azithromycin C_{min} levels required 5 to 7 days to reach steady-state.

When studied in healthy elderly subjects from age 65 to 85 years, the pharmacokinetic parameters of azithromycin in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred.

The high values in adults for apparent steady-state volume of distribution (31.1 L/kg) and plasma clearance (630 mL/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues.

Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in the following table:

AZITHROMYCIN CONCENTRATIONS FOLLOWING TWO–250 mg (500 mg) CAPSULES IN ADULTS

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION (μg/g or μg/mL)[1]
SKIN	72–96	0.4
LUNG	72–96	4.0
SPUTUM*	2–4	1.0
SPUTUM**	10–12	2.9
TONSIL***	9–18	4.5
TONSIL***	180	0.9
CERVIX****	19	2.8

TISSUE OR FLUID	CORRESPONDING PLASMA OR SERUM LEVEL (μg/mL)	TISSUE (FLUID) PLASMA (SERUM) RATIO[1]
SKIN	0.012	35
LUNG	0.012	> 100
SPUTUM*	0.64	2
SPUTUM**	0.1	30
TONSIL***	0.03	> 100
TONSIL***	0.006	> 100
CERVIX****	0.04	70

[1] High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of azithromycin is pH related. Azithromycin is concentrated in cell lysosomes which have a low intraorganelle pH, at which the drug's activity is reduced. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

* Sample was obtained 2–4 hours after the first dose.

** Sample was obtained 10–12 hours after the first dose.

*** Dosing regimen of 2 doses of 250 mg each, separated by 12 hours.

**** Sample was obtained 19 hours after a single 500 mg dose.

The extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Continued on next page

Information for Patients: Patients should be warned about engaging in activities requiring mental alertness, such as driving a car or operating dangerous machinery.

Drug Interactions: Antihistamines have additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, antianxiety agents, etc.). MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines. MAO inhibitors may enhance the effect of phenylpropanolamine. Sympathomimetics may reduce the effects of antihypertensive drugs.

Carcinogenesis, Mutagenesis: Long-term studies in animals to evaluate carcinogenic and mutagenic potential have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with Dimetane-DC Cough Syrup. It is also not known whether Dimetane-DC Cough Syrup can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Dimetane-DC Cough Syrup should be given to a pregnant woman only if clearly needed.

Reproduction studies of brompheniramine maleate (one of the components of the Dimetane formulations) in rats and mice at doses up to 16 times the maximum human dose have revealed no evidence of impaired fertility or harm to the fetus.

Nursing Mothers: Because of the higher risk of intolerance of antihistamines in small infants generally, and in newborns and prematures in particular, and the fact that codeine appears in human milk, Dimetane-DC Cough Syrup is contraindicated in nursing mothers.

ADVERSE REACTIONS

The most frequent adverse reactions to Dimetane-DC Cough Syrup are: sedation; dryness of mouth, nose and throat; thickening of bronchial secretions; dizziness. Other adverse reactions may include:

Dermatologic: Urticaria, drug rash, photosensitivity, pruritus.

Cardiovascular System: Hypotension, hypertension, cardiac arrhythmias.

CNS: Disturbed coordination, tremor, irritability, insomnia, visual disturbances, weakness, nervousness, convulsions, headache, euphoria, and dysphoria.

G. U. System: Urinary frequency, difficult urination.

G. I. System: Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Tightness of chest and wheezing, shortness of breath. At higher doses, codeine has most of the disadvantages of morphine including respiratory depression.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

DRUG ABUSE AND DEPENDENCE

Codeine can produce drug dependence of the morphine type, and therefore has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Dimetane-DC Cough Syrup is subject to the Federal Controlled Substances Act (Schedule V).

OVERDOSAGE

Signs and Symptoms: Serious overdose with codeine is characterized by respiratory depression, extreme somnolence progressing to stupor or coma. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The central nervous system effects from overdosage of brompheniramine may vary from depression to stimulation. Anticholinergic effects may also occur. Overdosage of phenylpropanolamine may be associated with tachycardia, hypertension and cardiac arrhythmias.

Toxic Doses: Doses of 800 mg or more of codeine have caused partial loss of consciousness, delirium, restlessness, excitement, tremors, convulsions and collapse; or respiratory paralysis with such sequelae as mydriasis, marked vasodilatation, and finally death. A $2^1/_2$-year-old child survived a dose of 300–900 mg of brompheniramine; the lethal dose of phenylpropanolamine is in the range of 50 mg/kg.

Treatment: Respiratory depression should be treated promptly. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. If necessary, reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation must be provided. The narcotic antagonist, naloxone, is a specific antidote to codeine-induced respiratory depression, and should be administered by the intravenous route if appropriate (see package insert for naloxone). Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under constant surveillance.

Gastric emptying may be useful in removing unabsorbed drug, either by inducing emesis or lavage; precautions against aspiration must be taken. Stimulants or depressants should be used cautiously and only when specifically indicated. If marked excitement is present, one of the short-acting barbiturates or chloral hydrate may be used.

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age and over: 2 teaspoonfuls every 4 hours. Children 6 to under 12 years: 1 teaspoonful every 4 hours. Children 2 to under 6 years: $^1/_2$ teaspoonful every 4 hours. Use of codeine-containing preparations is not recommended for children under 2 years of age.

Do not exceed 6 doses during a 24-hour period.

HOW SUPPLIED

Dimetane-DC Cough Syrup is a light bluish-pink syrup containing in each 5 mL (1 teaspoonful): brompheniramine maleate 2 mg, phenylpropanolamine HCl 12.5 mg, and codeine phosphate 10 mg; available in pints (NDC 0031-1833-25).

Store at controlled room temperature, between 15°C and 30°C (59°F and 86°F).

Dispense in tight, light-resistant container.

DIMETANE®-DX

℞

[*di 'mĕ-tān*]

COUGH SYRUP

SUGAR-FREE

DESCRIPTION

Dimetane-DX Cough Syrup is a light-red syrup with a butterscotch flavor.

Each 5 mL (1 teaspoonful) contains:

Brompheniramine Maleate, USP	2 mg
Pseudoephedrine Hydrochloride, USP	30 mg
Dextromethorphan Hydrobromide, USP	10 mg
Alcohol 0.95 percent	

In a palatable, aromatic vehicle.

Inactive Ingredients: Citric Acid, FD&C Red 40, FD&C Yellow 6, Flavors, Glycerin, Saccharin Sodium, Sodium Benzoate, Sorbitol, Water.

Antihistamine/Nasal Decongestant/Antitussive syrup for oral administration.

CLINICAL PHARMACOLOGY

Brompheniramine maleate is a histamine antagonist, specifically an H_1-receptor-blocking agent belonging to the alkylamine class of antihistamines. Antihistamines appear to compete with histamine for receptor sites on effector cells. Brompheniramine also has anticholinergic (drying) and sedative effects. Among the antihistaminic effects, it antagonizes the allergic response (vasodilatation, increased vascular permeability, increased mucus secretion) of nasal tissue. Brompheniramine is well absorbed from the gastrointestinal tract, with peak plasma concentration after single, oral dose of 4 mg reached in 5 hours; urinary excretion is the major route of elimination, mostly as products of biodegradation; the liver is assumed to be the main site of metabolic transformation.

Pseudoephedrine acts on sympathetic nerve endings and also on smooth muscle, making it useful as a nasal decongestant. The nasal decongestant effect is mediated by the action of pseudoephedrine on α-sympathetic receptors, producing vasoconstriction of the dilated nasal arterioles. Following oral administration, effects are noted within 30 minutes with peak activity occurring at approximately one hour.

Dextromethorphan acts centrally to elevate the threshold for coughing. It has no analgesic or addictive properties. The onset of antitussive action occurs in 15 to 30 minutes after administration and is of long duration.

INDICATIONS AND USAGE

For relief of coughs and upper respiratory symptoms, including nasal congestion, associated with allergy or the common cold.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients. Do not use in the newborn, in premature infants, in nursing mothers, in patients with severe hypertension or severe coronary artery disease, or in those receiving monoamine oxidase (MAO) inhibitors.

Antihistamines should not be used to treat lower respiratory tract conditions including asthma.

WARNINGS

Especially in infants and small children, antihistamines in overdosage may cause hallucinations, convulsions, and death.

Antihistamines may diminish mental alertness. In the young child, they may produce excitation.

PRECAUTIONS

General: Because of its antihistamine component, Dimetane-DX Cough Syrup should be used with caution in patients with a history of bronchial asthma, narrow angle glaucoma, gastrointestinal obstruction, or urinary bladder neck obstruction. Because of its sympathomimetic component, Dimetane-DX Cough Syrup should be used with caution in patients with diabetes, hypertension, heart disease, or thyroid disease.

Information for Patients: Patients should be warned about engaging in activities requiring mental alertness, such as driving a car or operating dangerous machinery.

Drug Interactions: Antihistamines have additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, antianxiety agents, etc.). MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines. MAO inhibitors may enhance the effect of pseudoephedrine. Sympathomimetics may reduce the effects of antihypertensive drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies of Dimetane-DX Cough Syrup to assess the carcinogenic and mutagenic potential or the effect on fertility have not been performed.

Pregnancy

Teratogenic Effects —Pregnancy Category C

Animal reproduction studies have not been conducted with Dimetane-DX Cough Syrup. It is also not known whether Dimetane-DX Cough Syrup can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Dimetane-DX Cough Syrup should be given to a pregnant woman only if clearly needed.

Reproduction studies of brompheniramine maleate (a component of Dimetane-DX Cough Syrup) in rats and mice at doses up to 16 times the maximum human dose have revealed no evidence of impaired fertility or harm to the fetus.

Nursing Mothers: Because of the higher risk of intolerance of antihistamines in small infants generally, and in newborns and prematures in particular, Dimetane-DX Cough Syrup is contraindicated in nursing mothers.

ADVERSE REACTIONS

The most frequent adverse reactions to Dimetane-DX Cough Syrup are: sedation; dryness of mouth, nose and throat; thickening of bronchial secretions; dizziness. Other adverse reactions may include:

Dermatologic: Urticaria, drug rash, photosensitivity, pruritus.

Cardiovascular System: Hypotension, hypertension, cardiac arrhythmias, palpitation.

CNS: Disturbed coordination, tremor, irritability, insomnia, visual disturbances, weakness, nervousness, convulsions, headache, euphoria, and dysphoria.

G. U. System: Urinary frequency, difficult urination.

G. I. System: Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Tightness of chest and wheezing, shortness of breath.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

OVERDOSAGE

Signs and Symptoms: Central nervous system effects from overdosage of brompheniramine may vary from depression to stimulation, especially in children. Anticholinergic effects may be noted. Toxic doses of pseudoephedrine may result in CNS stimulation, tachycardia, hypertension, and cardiac arrhythmias; signs of CNS depression may occasionally be seen. Dextromethorphan in toxic doses will cause drowsiness, ataxia, nystagmus, opisthotonos, and convulsive seizures.

Toxic Doses: Data suggest that individuals may respond in an unexpected manner to apparently small amounts of a particular drug. A $2^1/_2$-year-old child survived the ingestion of 21 mg/kg of dextromethorphan exhibiting only ataxia, drowsiness, and fever, but seizures have been reported in 2 children following the ingestion of 13–17 mg/kg. Another $2^1/_2$-year-old child survived a dose of 300–900 mg of brompheniramine. The toxic dose of pseudoephedrine should be less than that of ephedrine, which is estimated to be 50 mg/kg.

Treatment: Induce emesis if patient is alert and is seen prior to 6 hours following ingestion. Precautions against aspiration must be taken, especially in infants and small children. Gastric lavage may be carried out, although in some instances tracheostomy may be necessary prior to lavage. Naloxone hydrochloride 0.005 mg/kg intravenously may be of value in reversing the CNS depression that may occur from an overdose of dextromethorphan. CNS stimulants may counter CNS depression. Should CNS hyperactivity or convulsive seizures occur, intravenous short-acting barbiturates may be indicated. Hypertensive responses and/or tachycardia should be treated appropriately. Oxygen, intravenous fluids, and other supportive measures should be employed as indicated.

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age and over: 2 teaspoonfuls every 4 hours. Children 6 to under 12 years: 1 teaspoonful every 4 hours. Children 2 to under 6 years: $^1/_2$ teaspoonful every 4 hours. Children 6 months to under 2 years: Dosage to be established by physician.

Do not exceed 6 doses during a 24-hour period.

Continued on next page

A. H. Robins—Cont.

HOW SUPPLIED

Dimetane-DX Cough Syrup is a light-red syrup containing in each 5 mL (1 teaspoonful) brompheniramine maleate 2 mg, pseudoephedrine hydrochloride 30 mg and dextromethorphan hydrobromide 10 mg, available in pints (NDC 0031-1836-25) and gallons (NDC 0031-1836-29).

Store at controlled room temperature, between 15°C and 30°C (59°F and 86°F).

Dispense in tight, light-resistant container.

DONNATAL® TABLETS ℞
DONNATAL® CAPSULES ℞
DONNATAL® ELIXIR ℞

[*don'nă-tal*]

DESCRIPTION

Each Donnatal tablet, capsule or 5 mL (teaspoonful) of elixir (23% alcohol) contains:

Phenobarbital, USP (Warning: May be habit forming)	16.2 mg
Hyoscyamine Sulfate, USP	0.1037 mg
Atropine Sulfate, USP	0.0194 mg
Scopolamine Hydrobromide, USP	0.0065 mg

INACTIVE INGREDIENTS:

Tablets: Dibasic Calcium Phosphate, Magnesium Stearate, Microcrystalline Cellulose, Silicon Dioxide, Sodium Starch Glycolate, Stearic Acid, Sucrose. May contain Corn Starch, Dextrose, or Invert Sugar.

Capsules: Corn Starch, Edible Ink, D&C Yellow 10 and FD&C Green 3 or FD&C Blue 1 and FD&C Yellow 6, FD&C Blue 2 Aluminum Lake, Gelatin, Lactose, Sucrose. May contain FD&C Red 40 and Yellow 6 Aluminum Lakes.

Elixir: D&C Yellow 10, FD&C Blue 1, FD&C Yellow 6, Flavors, Glucose, Saccharin Sodium, Water.

ACTIONS

This drug combination provides natural belladonna alkaloids in a specific, fixed ratio combined with phenobarbital to provide peripheral anticholinergic/antispasmodic action and mild sedation.

INDICATIONS

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the following indications as "possibly" effective:

For use as adjunctive therapy in the treatment of irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

May also be useful as adjunctive therapy in the treatment of duodenal ulcer. IT HAS NOT BEEN SHOWN CONCLUSIVELY WHETHER ANTICHOLINERGIC/ANTISPASMODIC DRUGS AID IN THE HEALING OF A DUODENAL ULCER, DECREASE THE RATE OF RECURRENCES OR PREVENT COMPLICATIONS.

CONTRAINDICATIONS

Glaucoma, obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis, etc.); paralytic ileus, intestinal atony of the elderly or debilitated patient; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis especially if complicated by toxic megacolon; myasthenia gravis; hiatal hernia associated with reflux esophagitis.

Donnatal is contraindicated in patients with known hypersensitivity to any of the ingredients. Phenobarbital is contraindicated in acute intermittent porphyria and in those patients in whom phenobarbital produces restlessness and/or excitement.

WARNINGS

In the presence of a high environmental temperature, heat prostration can occur with belladonna alkaloids (fever and heatstroke due to decreased sweating).

Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful.

Donnatal may produce drowsiness or blurred vision. The patient should be warned, should these occur, not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery, and not to perform hazardous work.

Phenobarbital may decrease the effect of anticoagulants, and necessitate larger doses of the anticoagulant for optimal effect. When the phenobarbital is discontinued, the dose of the anticoagulant may have to be decreased.

Phenobarbital may be habit forming and should not be administered to individuals known to be addiction prone or to those with a history of physical and/or psychological dependence upon drugs.

Since barbiturates are metabolized in the liver, they should be used with caution and initial doses should be small in patients with hepatic dysfunction.

PRECAUTIONS

Use with caution in patients with: autonomic neuropathy, hepatic or renal disease, hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, tachycardia, and hypertension.

Belladonna alkaloids may produce a delay in gastric emptying (antral stasis) which would complicate the management of gastric ulcer.

Theoretically, with overdosage, a curare-like action may occur.

CARCINOGENESIS, MUTAGENESIS. Long-term studies in animals have not been performed to evaluate carcinogenic potential.

PREGNANCY CATEGORY C. Animal reproduction studies have not been conducted with Donnatal. It is not known whether Donnatal can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Donnatal should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Donnatal is administered to a nursing mother.

ADVERSE REACTIONS

Adverse reactions may include xerostomia; urinary hesitancy and retention; blurred vision; tachycardia; palpitation; mydriasis; cycloplegia; increased ocular tension; loss of taste sense; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; musculoskeletal pain; severe allergic reaction or drug idiosyncrasies, including anaphylaxis, urticaria and other dermal manifestations; and decreased sweating. Elderly patients may react with symptoms of excitement, agitation, drowsiness, and other untoward manifestations to even small doses of the drug.

Phenobarbital may produce excitement in some patients, rather than a sedative effect. In patients habituated to barbiturates, abrupt withdrawal may produce delirium or convulsions.

DOSAGE AND ADMINISTRATION

The dosage of Donnatal should be adjusted to the needs of the individual patient to assure symptomatic control with a minimum of adverse effects.

Donnatal Tablets or Capsules. Adults: One or two Donnatal tablets or capsules three or four times a day according to condition and severity of symptoms.

Donnatal Elixir. Adults: One or two teaspoonfuls of elixir three or four times a day according to conditions and severity of symptoms.

Children (Elixir)—may be dosed every 4 or 6 hours.:

Body Weight	Starting Dosage q4h	Starting Dosage q6h
10 lb (4.5 kg)	0.5 mL	0.75 mL
20 lb (9.1 kg)	1.0 mL	1.5 mL
30 lb (13.6 kg)	1.5 mL	2.0 mL
50 lb (22.7 kg)	1/2 tsp	3/4 tsp
75 lb (34.0 kg)	3/4 tsp	1 tsp
100 lb (45.4 kg)	1 tsp	1 1/2 tsp

OVERDOSAGE

The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot and dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. If indicated, parenteral cholinergic agents such as physostigmine or bethanechol chloride, should be added.

HOW SUPPLIED

Donnatal® Tablets. White, compressed, scored and embossed "R"; in bottles of 100 (NDC 0031-4250-63), 1000 (NDC 0031-4250-74) and Dis-Co® Unit Dose Packs of 100 (NDC 0031-4250-64).

Donnatal® Capsules. Green and white, monogrammed "AHR" and "4207"; in bottles of 100 (NDC 0031-4207-63).

Donnatal® Elixir. Green, citrus flavored, in 4 fl. oz. (NDC 0031-4221-12), pints (NDC 0031-4221-25), gallons (NDC 0031-4221-29) and 5 mL Dis-Co® Unit Dose Packs (4 × 25s) (NDC 0031-4221-13).

Store at controlled room temperature, between 20°C and 25°C (68°F and 77°F).

Dispense in tight, light-resistant container.

Shown in Product Identification Guide, page 331

DONNATAL EXTENTABS®

[*don'nă-tal ĕks"tĕn'tabs*]

DESCRIPTION

Each Donnatal Extentabs tablet contains:

Phenobarbital, USP (3/4 gr) (Warning: May be habit forming)	
Hyoscyamine Sulfate, USP	0.311[illegible] mg
Atropine Sulfate, USP	0.0582 mg
Scopolamine Hydrobromide, USP	0.019[illegible] mg

Each Donnatal Extentabs tablet contains the equivalent of three Donnatal tablets. Extentabs are designed to release the ingredients gradually to provide effects for up to twelve (12) hours.

Inactive Ingredients: Acacia, Acetylated Monoglycerides, Calcium Sulfate, Carnauba Wax, D&C Yellow 10, Edible Ink, FD&C Blue 1, FD&C Blue 2 Aluminum Lake, FD&C Yellow 6, Gelatin, Guar Gum, Magnesium Stearate, Polysorbate, Shellac, Sodium Phosphate, Sucrose, Titanium Dioxide, Wheat Flour, White Wax and other ingredients, one of which is a corn derivative. May include FD&C Red 40 and Yellow 6 Aluminum Lakes.

ACTIONS

This drug combination provides natural belladonna alkaloids in a specific, fixed ratio combined with phenobarbital to provide peripheral anticholinergic/antispasmodic action and mild sedation.

INDICATIONS

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the following indications as "possibly" effective:

For use as adjunctive therapy in the treatment of irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

May also be useful as adjunctive therapy in the treatment of duodenal ulcer. IT HAS NOT BEEN SHOWN CONCLUSIVELY WHETHER ANTICHOLINERGIC/ANTISPASMODIC DRUGS AID IN THE HEALING OF A DUODENAL ULCER, DECREASE THE RATE OF RECURRENCES OR PREVENT COMPLICATIONS.

CONTRAINDICATIONS

Glaucoma, obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis, etc.); paralytic ileus, intestinal atony of the elderly or debilitated patient; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis especially if complicated by toxic megacolon; myasthenia gravis; hiatal hernia associated with reflux esophagitis.

Donnatal is contraindicated in patients with known hypersensitivity to any of the ingredients. Phenobarbital is contraindicated in acute intermittent porphyria and in those patients in whom phenobarbital produces restlessness and/or excitement.

WARNINGS

In the presence of a high environmental temperature, heat prostration can occur with belladonna alkaloids (fever and heatstroke due to decreased sweating).

Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful.

Donnatal may produce drowsiness or blurred vision. The patient should be warned, should these occur, not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery, and not to perform hazardous work.

Phenobarbital may decrease the effect of anticoagulants and necessitate larger doses of the anticoagulant for optimal effect. When the phenobarbital is discontinued, the dose of the anticoagulant may have to be decreased.

Phenobarbital may be habit forming and should not be administered to individuals known to be addiction prone or to those with a history of physical and/or psychological dependence upon drugs.

Since barbiturates are metabolized in the liver, they should be used with caution and initial doses should be small in patients with hepatic dysfunction.

PRECAUTIONS

Use with caution in patients with: autonomic neuropathy, hepatic or renal disease, hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, tachycardia, and hypertension.

Belladonna alkaloids may produce a delay in gastric emptying (antral stasis) which would complicate the management of gastric ulcer.

duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

Steroid therapy should be administered with caution in patients with severe ulcerative disease because these patients are predisposed to perforation of the bowel wall. Where surgery is imminent, it is hazardous to wait more than a few days for a satisfactory response to medical treatment. General precautions common to all corticosteroid therapy should be observed during treatment with CORTIFOAM. These include gradual withdrawal of therapy to allow for possible adrenal insufficiency and awareness to possible growth suppression in children. Patients should be kept under close observation, for, as with all drugs, rare individuals may react unfavorably under certain conditions. If severe reactions or idiosyncrasies occur, steroids should be discontinued immediately and appropriate measures instituted. Do not employ in immediate or early postoperative period following ileorectostomy.

Information for patients: Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

ADVERSE REACTIONS

Corticosteroid therapy may produce side effects which include moon face, fluid retention, excessive appetite and weight gain, abnormal fat deposits, mental symptoms, hypertrichosis, acne, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, menstrual disorders, neuropathy, peptic ulcer, decreased glucose tolerance, hypokalemia, adrenal insufficiency, necrotizing angiitis, hypertension, pancreatitis and increased intraocular pressure. In children, suppression of growth may occur. Increased intracranial pressure may occur and possibly account for headache, insomnia and fatigue. Subcapsular cataracts may result from prolonged usage. Long-term use of all corticosteroids results in catabolic effects characterized by negative protein and calcium balance. Osteoporosis, spontaneous fractures and aseptic necrosis of the hip and humerus may occur as part of this catabolic phenomenon. Where hypopotassemia and other symptoms associated with fluid and electrolyte imbalance call for potassium supplementation and salt poor or salt-free diets, these may be instituted and are compatible with diet requirements for ulcerative proctitis.

ADMINISTRATION AND DOSAGE

Usual dose is one applicatorful once or twice daily for two or three weeks, and every second day thereafter, administered rectally. The patient direction package with the applicator describes how to use the aerosol container and applicator. Satisfactory response usually occurs within five to seven days marked by a decrease in symptoms. Symptomatic improvement in ulcerative proctitis should not be used as the sole criterion for evaluating efficacy. Sigmoidoscopy is also recommended to judge dosage adjustment, duration of therapy and rate of improvement.

DIRECTIONS FOR USE

1) Shake foam container vigorously before use. Hold container upright and insert into the opening of the tip of the applicator. **Be sure applicator plunger is drawn all the way back.** Container must be held upright to obtain proper flow of medication. 2) To fill, press down slowly on container cap. When foam reaches fill line in the applicator, it is ready for use. **Caution:** The aerosol container should never be inserted directly into the anus. 3) Remove applicator from container. Allow some foam to remain on the applicator tip. Hold applicator by barrel and gently insert tip into the anus. With applicator in place, push plunger in order to expel foam, then withdraw applicator. (Applicator parts should be pulled apart for thorough cleaning with warm water.)

HOW SUPPLIED

CORTIFOAM (NDC 0021-0695-20) is supplied in an aerosol container with a special rectal applicator. Each applicator delivers approximately 900 mg of foam containing approximately 90 mg of hydrocortisone as 90 mg of hydrocortisone acetate. The aerosol container will deliver a minimum of 14 applications.

Store upright at controlled room temperature 15°–30°C (59°–86°F).

CAUTION

Federal law prohibits dispensing without prescription.

Shown in Product Identification Guide, page 334

DEPONIT® ℞

[dĕp'ō-nit]

(nitroglycerin transdermal delivery system)

DESCRIPTION

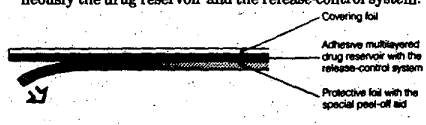
Nitroglycerin is 1,2,3-propanetriol trinitrate, an organic nitrate whose structural formula is:

and whose molecular weight is 227.09. The organic nitrates are vasodilators, active on both arteries and veins.

The Deponit® transdermal system is a flat unit designed to provide continuous controlled release of nitroglycerin through intact skin. The rate of release of nitroglycerin is linearly dependent upon the area of the applied system; each cm^2 of applied system delivers approximately 0.013 mg of nitroglycerin per hour. Thus, the 16 cm^2 and 32 cm^2 systems deliver approximately 0.2 and 0.4 mg of nitroglycerin per hour, respectively. The remainder of the nitroglycerin in each system serves as a reservoir and is not delivered in normal use. After 12 hours, for example, each system has delivered 15% of its original content of nitroglycerin. Deponit contains nitroglycerin in a matrix composed of lactose, plasticizer, medical adhesive, polyisobutylene and aluminized plastic for controlled release of the active agent through the skin into the systemic circulation. The 16 cm^2 and 32 cm^2 systems contain 16 mg and 32 mg of nitroglycerin, respectively.

The Deponit system is approximately 0.3 mm thick, insoluble in water, and, as illustrated below, consists of two main elements:

1. A flexible, flesh-colored waterproof covering foil.
2. A multilayered adhesive film that constitutes simultaneously the drug reservoir and the release-control system.



The system is protected by an aluminum foil which has a patented S-shaped opening to facilitate its removal prior to use of the system. Prior to use, the protective foil is removed from the adhesive surface.

CLINICAL PHARMACOLOGY

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction and coronary dilatation remains undefined. Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the anti-anginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.

Pharmacokinetics: The volume of distribution of nitroglycerin is about 3 L/kg, and nitroglycerin is cleared from this volume at extremely rapid rates, with a resulting serum half-life of about 3 minutes. The observed clearance rates (close to 1 L/kg/min) greatly exceed hepatic blood flow; known sites of extrahepatic metabolism include red blood cells and vascular walls. The first products in the metabolism of nitroglycerin are inorganic nitrate and the 1,2- and 1,3-dinitroglycerols. The dinitrates are less effective vasodilators than nitroglycerin, but they are longer-lived in the serum, and their net contribution to the overall effect of chronic nitroglycerin regimens is not known. The dinitrates are further metabolized to (non-vasoactive) mononitrates and, ultimately, to glycerol and carbon dioxide. To avoid development of tolerance to nitroglycerin, drug-free intervals of 10–12 hours are known to be sufficient; shorter intervals have not been well studied. In one well-controlled clinical trial, subjects receiving nitroglycerin appeared to exhibit a rebound or withdrawal effect, so that their exercise tolerance at the end of the daily drug-free interval was *less* than that exhibited by the parallel group receiving placebo. In healthy volunteers, steady-state plasma concentrations of nitroglycerin are reached by about two hours after application of a patch and are maintained for the duration of wearing the system (observations have been limited to 24 hours). Upon removal of the patch, the plasma concentration declines with a half-life of about an hour.

Clinical trials: Regimens in which nitroglycerin patches were worn for 12 hours daily have been studied in well-controlled trials up to 4 weeks in duration. Starting about 2 hours after application and continuing until 10–12 hours after application, patches that deliver at least 0.4 mg of nitroglycerin per hour have consistently demonstrated greater anti-anginal activity than placebo. Lower-dose patches have not been as well studied, but in one large, well-controlled trial in which higher-dose patches were also studied, patches delivering 0.2 mg/hr had significantly *less* anti-anginal activity than placebo. It is reasonable to believe that the rate of nitroglycerin absorption from patches may vary with the site of application, but this relationship has not been adequately studied. The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

INDICATIONS AND USAGE

Transdermal nitroglycerin is indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute attack.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

WARNINGS

The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia. A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a Deponit patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS

General:

Severe hypotension, particularly with upright posture, may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy. As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted. In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence. Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10–12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients demonstrated decreased exercise tolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is unknown.

Information for Patients:

Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy. Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol. After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets. A patient leaflet is supplied with the systems.

Continued on next page

Schwarz Pharma, Inc.—Cont.

Nitroglycerin Transdermal Rated Release in vivo	Total Nitroglycerin in System	System Size	Carton Size	NDC
0.2 mg/hr	16 mg	16 cm^2	30	0091-4195-01
			30*	0091-4195-31
			100*	0091-4195-11
0.4 mg/hr	32 mg	32 cm^2	30	0091-4196-01
			30*	0091-4196-31
			100*	0091-4196-11

*Institutional Package

Drug Interactions:
The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.
Carcinogenesis, Mutagenesis, Impairment of Fertility:
Studies to evaluate the carcinogenic or mutagenic potential of nitroglycerin have not been performed. Nitroglycerin's effect upon reproductive capacity is similarly unknown.
Pregnancy—Pregnancy Category C:
Animal reproduction studies have not been conducted with nitroglycerin. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or whether it can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.
Nursing Mothers:
It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.
Pediatric use:
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.
Allergic reactions to nitroglycerin are also uncommon, and the great majority of those reported have been cases of contact dermatitis or fixed drug eruptions in patients receiving nitroglycerin in ointments or patches. There have been a few reports of genuine anaphylactoid reactions, and these reactions can probably occur in patients receiving nitroglycerin by any route.
Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients; for further discussion of its diagnosis and treatment see OVERDOSAGE.
Application-site irritation may occur but is rarely severe.
In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

	placebo	patch
headache	18%	63%
lightheadedness	4%	6%
hypotension and/or syncope	0%	4%
increased angina	2%	2%

OVERDOSAGE:

Hemodynamic Effects:
The ill effects of nitroglycerin overdose are generally the results of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever, vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.
Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose. No data are available to suggest physiological maneuvers (e.g. maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which—if any—of these substances can usefully be removed from the body by hemodialysis. No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary. The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good. In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.
Methemoglobinemia:
Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant ($\geq 10\%$) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2–4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo. Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1–2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

The suggested starting dose is between 0.2 mg/hr and 0.4 mg/hr. Doses between 0.4 mg/hr and 0.8 mg/hr have shown continued effectiveness for 10–12 hours daily for at least one month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10–12 hrs is sufficient (see CLINICAL PHARMACOLOGY). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12–14 hours and a daily patch-off period of 10–12 hours. Although some well controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e., complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

HOW SUPPLIED

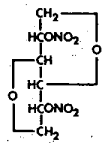
Deponit® (nitroglycerin transdermal delivery system) is packaged in cartons containing unit doses of flesh-colored systems on aluminum backings. See table below.
[See table above.]
Store at room temperature not above 25° C (77° F). Do not refrigerate.
CAUTION: Federal law prohibits dispensing without prescription.
Shown in Product Identification Guide, page 334

DILATRATE®-SR

[*dī'lă-trāt*]
(isosorbide dinitrate)
Sustained Release Capsules
40 mg

DESCRIPTION

Isosorbide dinitrate (ISDN) is 1,4:3,6-dianhydro-D-glucitol 2,5 dinitrate, an organic nitrate whose structural formula is [See chemical structure at top of next column.]
and whose molecular weight is 236.14. The organic nitrates are vasodilators, active on both arteries and veins. Each Dilatrate-SR sustained release capsule contains 40 mg of isosorbide dinitrate, in a microdialysis delivery system that causes the active drug to be released over an extended period. Each capsule also contains ethylcellulose, lactose, pharmaceutical glaze, starch, sucrose and talc. The capsule shells contain D&C Red 33, D&C Yellow 10, gelatin and titanium dioxide.



CLINICAL PHARMACOLOGY

The principal pharmacological action of isosorbide dinitrate is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.
Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were no more effective than placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.
Pharmacokinetics: The kinetics of absorption of isosorbide dinitrate from Dilatrate-SR sustained release capsules have not been well studied. Studies of immediate-release formulations of ISDN have found highly variable bioavailability (10 to 90%), with extensive first-pass metabolism in the liver. Most such studies have observed progressive increases in bioavailability during chronic therapy; it is not known whether similar increases in bioavailability appear during the course of chronic therapy with Dilatrate-SR sustained release capsules.
Once absorbed, the distribution volume of isosorbide dinitrate is 2–4 L/kg and this volume is cleared at the rate of 2–4 L/min, so ISDN's half-life in serum is about an hour. Since the clearance exceeds hepatic blood flow, considerable extrahepatic metabolism must also occur. Clearance is affected primarily by denitration to the 2-mononitrate (15 to 25%) and the 5- mononitrate (75 to 85%).
Both metabolites have biological activity, especially the 5-mononitrate. With an overall half-life of about 5 hours, the 5-mononitrate is cleared from the serum by denitration to isosorbide; glucuronidation to the 5-mononitrate glucuronide; and denitration/hydration to sorbitol. The 2-mononitrate has been less well studied, but it appears to participate in the same metabolic pathways, with a half-life of about 2 hours.
The interdosing interval sufficient to avoid tolerance in ISDN has not been well defined. Studies of nitroglycerin (an organic nitrate with a very short half-life) have shown that dosing intervals of 10–12 hours are usually sufficient to prevent or attenuate tolerance. Dosing intervals that have succeeded in avoiding tolerance during trials of moderate doses (e.g. 30 mg) of immediate release ISDN have generally been somewhat longer (at least 14 hours), but this is consistent with the longer half-lives of ISDN and its active metabolites. An interdosing interval sufficient to avoid tolerance with Dilatrate-SR has not been demonstrated. In an eccentric dosing study, 40 mg capsules of Dilatrate-SR were administered daily at 0800 and 1400 hours. After two weeks of this regimen, Dilatrate-SR was statistically indistinguishable from placebo. Thus, the necessary interdosing interval sufficient to avoid tolerance remains unknown, but it must be greater than 18 hours.
Few well-controlled clinical trials of organic nitrates have been designed to detect rebound or withdrawal effects. In one such trial, however, subjects receiving nitroglycerin had lost exercise tolerance at the end of the daily interdosing interval than the parallel group receiving placebo. The incidence, magnitude, and clinical significance of similar phenomena in patients receiving ISDN have not been studied.
Clinical trials: In clinical trials, extended-release oral isosorbide dinitrate has been administered in a variety of regimens, with total daily doses ranging from 40 to 160 mg. A controlled trial using a single 40 mg sustained-release oral dose of isosorbide dinitrate (Dilatrate-SR) has demonstrated effective reductions in exercise-related angina for up to a

SmithKline Beecham—Cont.

Weight		50 mg/kg/Day Divided into 3 Doses		50 mg/kg/Day Divided into 4 Doses	
Lbs	Kg	Approximate Single Dose mg/q8h	Vol. (mL) needed with dilution of 225 mg/mL	Approximate Single Dose mg/q6h	Vol. (mL) needed with dilution of 225 mg/mL
10	4.5	75 mg	0.35 mL	55 mg	0.25 mL
20	9.0	150 mg	0.70 mL	110 mg	0.50 mL
30	13.6	225 mg	1.00 mL	170 mg	0.75 mL
40	18.1	300 mg	1.35 mL	225 mg	1.00 mL
50	22.7	375 mg	1.70 mL	285 mg	1.25 mL

In children with mild to moderate renal impairment (creatinine clearance of 70 to 40 mL/min.), 60 percent of the normal daily dose given in equally divided doses every 12 hours should be sufficient. In patients with moderate impairment (creatinine clearance of 40 to 20 mL/min.), 25 percent of the normal daily dose given in equally divided doses every 12 hours should be adequate. Children with severe renal impairment (creatinine clearance of 20 to 5 mL/min.) may be given 10 percent of the normal daily dose every 24 hours. All dosage recommendations apply after an initial loading dose.

RECONSTITUTION

Preparation of Parenteral Solution

Parenteral drug products should be SHAKEN WELL when reconstituted, and inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solutions should be discarded. When reconstituted or diluted according to the instructions below, Ancef (sterile cefazolin sodium) is stable for 24 hours at room temperature or for 10 days if stored under refrigeration (5°C or 41°F). Reconstituted solutions may range in color from pale yellow to yellow without a change in potency.

Single-Dose Vials

For I.M. injection, I.V. direct (bolus) injection or I.V. infusion, reconstitute with Sterile Water for Injection according to the following table. SHAKE WELL.

Vial Size	Amount of Diluent	Approximate Concentration	Approximate Available Volume
500 mg	2.0 mL	225 mg/mL	2.2 mL
1 gram	2.5 mL	330 mg/mL	3.0 mL

Pharmacy Bulk Vials

Add Sterile Water for Injection, Bacteriostatic Water for Injection or Sodium Chloride Injection according to the table below. SHAKE WELL.

Vial Size	Amount of Diluent	Approximate Concentration	Approximate Available Volume
5 grams	23 mL	1 gram/5 mL	26 mL
	48 mL	1 gram/10 mL	51 mL
10 grams	45 mL	1 gram/5 mL	51 mL
	96 mL	1 gram/10 mL	102 mL

"Piggyback" Vials

Reconstitute with 50 to 100 mL of Sodium Chloride Injection or other I.V. solution listed under ADMINISTRATION. When adding diluent to vial, allow air to escape by using a small vent needle or by pumping the syringe. SHAKE WELL. Administer with primary I.V. fluids, as a single dose.

ADMINISTRATION

Intramuscular Administration—Reconstitute vials with Sterile Water for Injection according to the dilution table above. Shake well until dissolved. *Ancef* should be injected into a large muscle mass. Pain on injection is infrequent with *Ancef*.

Intravenous Administration—Direct (bolus) injection: Following reconstitution according to the above table, further dilute vials with approximately 5 mL Sterile Water for Injection. Inject the solution slowly over 3 to 5 minutes, directly or through tubing for patients receiving parenteral fluids (see list below).

Intermittent or continuous infusion: Dilute reconstituted *Ancef* in 50 to 100 mL of one of the following solutions:

- Sodium Chloride Injection, USP
- 5% or 10% Dextrose Injection, USP
- 5% Dextrose in Lactated Ringer's Injection, USP
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP
- Invert Sugar 5% or 10% in Sterile Water for Injection
- Ringer's Injection, USP
- 5% Sodium Bicarbonate Injection, USP

DIRECTIONS FOR USE OF ANCEF (CEFAZOLIN SODIUM INJECTION) GALAXY® CONTAINER (PL 2040 PLASTIC)

Ancef in Galaxy® Container (PL 2040 Plastic) is to be administered either as a continuous or intermittent infusion using sterile equipment.

Storage

Store in a freezer capable of maintaining a temperature of −20°C (−4°F).

Thawing of Plastic Container

Thaw frozen container at 25°C or 77°F or under refrigeration (5°C or 41°F). (DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.)

Check for minute leaks by squeezing container firmly. If leaks are detected, discard solution as sterility may be impaired.

Do not add supplementary medication.

The container should be visually inspected. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency is not affected. Agitate after solution has reached room temperature. If after visual inspection the solution remains cloudy or if an insoluble precipitate is noted or if any seals or outlet ports are not intact, the container should be discarded.

The thawed solution is stable for 30 days under refrigeration (5°C or 41°F) and 48 hours at 25°C or 77°F. Do not refreeze thawed antibiotics.

Use sterile equipment. It is recommended that the intravenous administration apparatus be replaced at least once every 48 hours.

CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for administration:

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

HOW SUPPLIED

Ancef (sterile cefazolin sodium)—supplied in vials equivalent to 500 mg or 1 gram of cefazolin; in "Piggyback" Vials for intravenous admixture equivalent to 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 5 grams or 10 grams of cefazolin.

Ancef (cefazolin sodium injection) as a frozen, iso-osmotic, sterile, nonpyrogenic solution in plastic containers—supplied in 50 mL single-dose containers equivalent to 500 mg or 1 gram of cefazolin. Dextrose Hydrous, USP, has been added to the above dosages to adjust osmolality (approximately 2.4 grams and 2 grams, respectively). Store at or below −20°C (−4°F). (See DIRECTIONS FOR USE OF ANCEF [CEFAZOLIN SODIUM INJECTION] GALAXY® CONTAINER [PL 2040 PLASTIC].)

As with other cephalosporins, *Ancef* tends to darken depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected. Before reconstitution protect from light and store between 15° and 30°C (59° and 86°F).

Ancef supplied as a frozen, iso-osmotic, sterile, nonpyrogenic solution in plastic containers is manufactured for SmithKline Beecham Pharmaceuticals by Baxter Healthcare Corporation, Deerfield, IL 60015.

Galaxy is a registered trademark of Baxter International Inc.

Veterans Administration /Military /PHS —500 mg/50 mL, frozen, 24's, 6505-01-274-9683; 1 gram/50 mL, frozen, 24's, 6505-01-237-8453

AF:L50

Shown in Product Identification Guide, page 336

ANDRODERM®

[an-drō-derm]

Testosterone Transdermal System

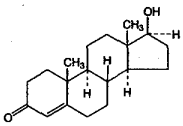
Controlled Delivery for Once-Daily Application

DESCRIPTION

Androderm (testosterone transdermal system) provides continuous delivery of testosterone (the primary endogenous androgen) for 24 hours following application to intact, nonscrotal skin (e.g., back, abdomen, thighs, upper arms).

Each *Androderm* system delivers in vivo 2.5 mg of testosterone per day across skin of average permeability.

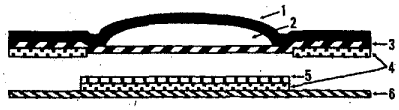
Androderm has a 7.5 cm^2 central drug delivery reservoir surrounded by a peripheral adhesive area. The total contact surface area is 37 cm^2. Each system contains 12.2 mg testosterone USP, dissolved in an alcohol-based gel. Testosterone USP is a white, or creamy white crystalline powder or crystals chemically described as 17β-hydroxyandrost-4-en-3-one.



Testosterone

$C_{19}H_{28}O_2$ mw 288.43

The *Androderm* system has six components as shown in Figure 1. Proceeding from the top toward the surface attached to the skin, the system is composed of (1) a transparent ethylene vinyl acetate copolymer/polyester laminate backing film, (2) a drug reservoir of testosterone USP, alcohol USP, glycerin USP, glycerol monooleate, and methyl laurate gelled with an acrylic acid copolymer, (3) a permeable polyethylene microporous membrane, and (4) a peripheral layer of acrylic adhesive surrounding the central, active drug delivery area of the system. Prior to opening of the system and application to the skin, the central delivery surface of the system is sealed with a peelable laminate disc (5) composed of a five-layer laminate containing polyester/polyesterurethane adhesive/aluminum foil/polyesterurethane adhesive/polyethylene. The disc is attached to and removed with the release liner (6), a silicone-coated polyester film, which is removed before the system can be used.



1. Backing Film
2. Drug Reservoir
3. Microporous Membrane
4. Adhesive
5. Disc
6. Release Liner

Figure 1: System Schematic

The active ingredient in the system is testosterone. The remaining components of the system are pharmacologically inactive.

CLINICAL PHARMACOLOGY

Androderm (testosterone transdermal system) delivers physiologic amounts of testosterone producing circulating testosterone concentrations that approximate the normal circadian rhythm of healthy young men.

Testosterone

Androderm (testosterone transdermal system) delivers testosterone, the primary androgenic hormone. Testosterone is responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; and alterations in body musculature and fat distribution.

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include the following: impotence and decreased sexual desire; fatigue and loss of energy; mood depression; and regression of secondary sexual characteristics.

General Androgen Effects

Androgens promote retention of nitrogen, sodium, potassium, and phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.

Androgens are also responsible for the growth spurt of adolescence and for the eventual termination of linear growth that is brought about by the fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates but may cause disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process.

Androgens have been reported to stimulate the production of red blood cells by enhancing erythropoietin production.

During exogenous administration of androgens, endogenous testosterone release is inhibited through feedback inhibition of pituitary LH secretion. With large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle stimulating hormone (FSH) secretion.

There is a lack of substantial evidence that androgens are effective in accelerating fracture healing or in shortening post-surgical convalescence.

Pharmacokinetics

Absorption

Following *Androderm* terone is continuous period. Daily applica PM results in a ser that mimics the no healthy young men (I occur in the early mo tions in the evening

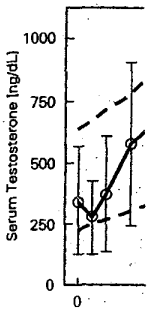


Figure 2: Mean (SD centrations during n hypogonadal male su shows the 95% confic tion observed in heal (t=0) at approximate

Table 1: Steady-stat parameters in hypog ous Androderm (test ment.

Parameter	Unit
C_{max}	ng/d
C_{avg}	ng/d
C_{min}	ng/d
T_{max}	hr
$T_{1/2}$	min
CL	L/da

C_{max} = maximum seru
C_{avg} = average serum
C_{min} = minimum seru
T_{max} = time of maxim
$T_{1/2}$ = elimination hal
CL = clearance

In a group of 34 hypo *droderm* systems to t arms resulted in avera over 24 hours. The ser during application wer plications to the chest individual variability 4 mg.

Table 2: Mean s (ng/dL) measured d 2 *Androderm* systems 34 hypogonadal men.

Sample Time (hr)	Abdomen Mean	SD
0	90	82
3	286	201
6	476	236
9	570	234
12	575	244
24	352	164

In a steady-state study cation of 1, 2, or 3 *And* in the mean morning These concentrations a the application of 1, 2, a baseline serum testost Normal range mornin are reached during the mulation of testosteror

Distribution

In serum, testosterone i none binding globulin (min. The albumin bou presumed to be bioacti considered to be bioact and the total testosterc tribution of bioactive a Bioactive serum testost during Androderm (test

Pharmacokinetics

Absorption

Following *Androderm* application to non-scrotal skin, testosterone is continuously absorbed during the 24-hour dosing period. Daily application of 2 systems at approximately 10 PM results in a serum testosterone concentration profile that mimics the normal circadian variation observed in healthy young men (Fig. 2 below). Maximum concentrations occur in the early morning hours with minimum concentrations in the evening (Table 1 below).

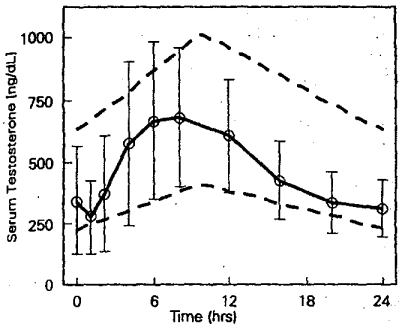


Figure 2: Mean (SD) steady state serum testosterone concentrations during nightly application of 2 systems in 29 hypogonadal male subjects. Area between the dashed lines shows the 95% confidence interval for the circadian variation observed in healthy young men.[1] System application (t=0) at approximately 10 PM.

Table 1: Steady-state serum testosterone pharmacokinetic parameters in hypogonadal men measured during continuous Androderm (testosterone transdermal system) treatment.

Parameter	Units	n	Mean	SD
C_{max}	ng/dL	56	753	276
C_{avg}	ng/dL	56	498	169
C_{min}	ng/dL	56	246	120
T_{max}	hr	56	7.9	2.2
$T_{1/2}$	min	29	71	32
CL	L/day	49	1304	464

C_{max}=maximum serum concentration
C_{avg}=average serum concentration (AUC/24 hr)
C_{min}=minimum serum concentration
T_{max}=time of maximum serum concentration
$T_{1/2}$=elimination half-life
CL=clearance

In a group of 34 hypogonadal men, application of two *Androderm* systems to the abdomen, back, thighs, or upper arms resulted in average testosterone absorption of 4 to 5 mg over 24 hours. The serum testosterone concentration profiles during application were similar for these sites (Table 2). Applications to the chest and shins resulted in greater interindividual variability and average 24 hour absorption of 3 to 4 mg.

Table 2: Mean serum testosterone concentrations (ng/dL) measured during single-dose applications of 2 *Androderm* systems applied at night to different sites in 34 hypogonadal men.

Sample Time (hr)	Abdomen Mean	Abdomen SD	Back Mean	Back SD	Thigh Mean	Thigh SD	Upper Arm Mean	Upper Arm SD
0	90	82	80	74	85	76	81	69
3	286	201	429	252	271	201	308	226
6	476	236	608	250	489	254	468	245
9	570	234	613	214	592	251	534	204
12	575	244	588	233	594	247	527	199
24	352	164	403	174	367	161	332	124

In a steady-state study of 12 hypogonadal men, nightly application of 1, 2, or 3 *Androderm* systems resulted in increases in the mean morning serum testosterone concentrations. These concentrations averaged 424, 584, and 766 ng/dL with the application of 1, 2, and 3 systems, respectively. The mean baseline serum testosterone concentration was 76 ng/dL. Normal range morning serum testosterone concentrations are reached during the first day of dosing. There is no accumulation of testosterone during continuous treatment.

Distribution

In serum, testosterone is bound with high affinity to sex hormone binding globulin (SHBG) and with low affinity to albumin. The albumin bound portion easily dissociates and is presumed to be bioactive. The SHBG-bound portion is not considered to be bioactive. The amount of SHBG in serum and the total testosterone concentration determine the distribution of bioactive and non-bioactive androgen.

Bioactive serum testosterone concentrations (BT) measured during Androderm (testosterone transdermal system) treatment paralleled the serum testosterone profile (Figure 2) and remained within the normal reference range.

Metabolism

Inactivation of testosterone occurs primarily in the liver. Testosterone (T) is metabolized to various 17-keto steroids through two different pathways, and the major active metabolites are estradiol (E2) and dihydrotestosterone (DHT). DHT binds with greater affinity to SHBG than does testosterone. In reproductive tissues, DHT is further metabolized to 3-alpha and 3-beta androstanediol.

In many tissues, the activity of testosterone appears to depend on reduction to DHT, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus, where it initiates transcription events and cellular changes related to androgen action.

During steady-state pharmacokinetic studies in hypogonadal men treated with *Androderm*, the average DHT:T and E2:T ratios were comparable to those in normal men, approximately 1:10 and 1:200, respectively.

Upon removal of the *Androderm* systems, serum testosterone concentrations decrease with an apparent half-life of approximately 70 minutes. Hypogonadal concentrations are reached within 24 hours following system removal.

Androderm therapy suppresses endogenous testosterone secretion via the pituitary/gonadal axis, resulting in a reduction in baseline serum testosterone concentrations compared to the untreated state.

Excretion

Approximately 90% of a testosterone dose given intramuscularly is excreted in the urine as glucuronide and sulfate conjugates of testosterone and its metabolites; about 6% is excreted in the feces, mostly in unconjugated form.

Special Populations

Geriatric

No age related effects on testosterone pharmacokinetics were observed in clinical trials of *Androderm* in men up to 65 years of age. In a group of 9 elderly testosterone deficient men (65–79 years of age, average baseline testosterone level 184±50 ng/dL), a single application of 2 *Androderm* systems to the back resulted in an average testosterone level of 591±121 ng/dL with a T_{max} of 14.2±4.2 hours. The total testosterone delivered over the 24-hour application time was 3.8±0.6 mg, approximately 20% less than the average amount delivered in younger patients.

Race

There is insufficient information available from *Androderm* trials to compare testosterone pharmacokinetics in different racial groups.

Renal Insufficiency

There is no experience with use of *Androderm* in patients with renal insufficiency.

Hepatic Insufficiency

There is no experience with use of *Androderm* in patients with hepatic insufficiency.

Drug-Drug Interactions

See "Precautions" below

Clinical Studies

In clinical studies, 93% of patients were treated with two *Androderm* systems daily, 6% used three systems daily, and 1% used one system daily.

The hormonal effects of Androderm (testosterone transdermal system) as a treatment for male hypogonadism were demonstrated in four open-label trials that included 94 hypogonadal men, ages 15 to 65 years. In these trials, *Androderm* produced average morning serum testosterone concentrations within the normal reference range in 92% of patients. The mean (SD) serum hormone concentrations and percentage of patients who achieved average concentrations within the normal ranges are shown in Table 3 below.

Table 3: Individual morning serum hormone concentrations (ng/dL) and percent of patients with mean concentrations within the normal range during continuous *Androderm* treatment (n=94).

Normal Range	T (306–1031)	BT (93–420)	DHT (28–85)	E2 (0.9–3.6)
Mean	589	312	47	2.7
SD	209	127	18	1.2
% Normal	92	88	85	77
% High	1	12	2	22
% Low	7	0	13	1

A physiological suppression of the pituitary/gonadal axis occurs during continuous *Androderm* treatment leading to reduced serum LH concentrations. In clinical trials, 10 of 21 (48%) of men with primary (hypergonadotropic) hypogonadism achieved normal range LH concentrations within 6 to 12 months of treatment. LH concentrations may remain elevated in some patients despite serum testosterone concentrations within the normal range.

Twenty-nine patients, previously treated with testosterone, completed 12 months of *Androderm* treatment. Following an 8-week androgen withdrawal period, *Androderm* treatment produced positive effects on fatigue, mood and sexual function. The percent of patients complaining of fatigue decreased from 79% to 10% during treatment ($p<0.001$). The average patient depression score (Beck Depression Inventory) decreased from 6.9 to 3.9 ($p<0.001$). Nocturnal penile tumescence and rigidity monitoring showed an increase in mean duration of erections 0.23 to 0.39 hours per night ($p=0.01$) and an increase in penile tip rigidity from 18% to 50% ($p<0.001$). The total number of self-reported erections reported increased from 2.3 to 7.8 per week ($p<0.001$).

Comparison with intramuscular testosterone: Sixty-six patients, previously treated with testosterone injections, received *Androderm* or intramuscular testosterone enanthate (200 mg every 2 weeks) treatment for 6 months. The percent of time that serum concentrations measured throughout the dosing interval remained within the normal range were as follows:

	Androderm	IM	*p* value
T	82%	72%	0.05
BT	87%	39%	<0.001
DHT	76%	70%	0.06
E2	81%	35%	<0.001

Sexual function was comparable between groups.

Effect on plasma lipids: In 67 men treated for 6 to 12 months, the average (SE) serum total cholesterol and HDL concentrations were 199 (7.6) ng/dL and 46 (2.3) ng/dL.

Compared to baseline values during a hypogonadal state achieved by 8 weeks of androgen withdrawal in 29 patients, the following changes in lipids were observed during 1 year of *Androderm* treatment: Cholesterol decreased 1.2%; HDL decreased 8%; Cholesterol/HDL ratio increased 9%. In these patients, lipids measured during *Androderm* treatment were not significantly different from those measured during prior IM injection treatment.

Effects on the prostate: Prostate size and serum prostate specific antigen (PSA) concentrations during treatment were comparable to values reported for eugonadal men. One case of prostate carcinoma occurred during *Androderm* treatment; two cases were detected during IM treatment.

INDICATIONS AND USAGE

Androderm (testosterone transdermal system) is indicated for testosterone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone.

Primary hypogonadism (congenital or acquired)—Testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations accompanied by gonadotropins (FSH, LH) above the normal range.

Secondary, i.e., hypogonadotropic hypogonadism (congenital or acquired)—idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low serum testosterone concentrations without associated elevation in gonadotropins. Appropriate adrenal cortical and thyroid hormone replacement therapy may be necessary in patients with multiple pituitary or hypothalamic abnormalities.

CONTRAINDICATIONS

Androgens are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate.

Androderm therapy has not been evaluated in women and must not be used in women. Testosterone may cause fetal harm.

Androderm is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with the development of peliosis hepatis, cholestatic jaundice and hepatic neoplasms, including hepatocellular carcinoma (see PRECAUTIONS, Carcinogenesis). Peliosis hepatis can be a life-threatening or fatal complication. Testosterone is not known to produce these adverse effects.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia. Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of subclinical or clinical prostate cancer prior to initiation of testosterone replacement therapy, be-

Continued on next page

SmithKline Beecham—Cont.

cause testosterone therapy may promote the growth of existing subclinical foci of prostate cancer.[2]
In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men (see PRECAUTIONS, Carcinogenesis).
Edema, with or without congestive heart failure, may be a serious complication of androgen treatment in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.
Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.

PRECAUTIONS

General
The physician should instruct patients to report any of the following side effects of androgens:
• Too frequent or persistent erections of the penis
• Any nausea, vomiting, jaundice, or ankle swelling
Virilization of female sexual partners has been reported with male use of a topical testosterone solution. Topically applied creams leave as much as 90 mg residual testosterone on the skin. The occlusive backing film on Androderm (testosterone transdermal system) prevents the partner from coming in contact with the active material in the system. Transfer of the system to the partner is unlikely.
Changes in body hair distribution, significant increase in acne, or other signs of virilization of the female partner should be brought to the attention of a physician.
Information for Patients
An information brochure is available for patients concerning the use of *Androderm*.
Advise patients of the following:
Androderm should not be applied to the scrotum.
Androderm should not be applied over a bony prominence or on a part of the body that could be subject to prolonged pressure during sleep or sitting. Application to these sites has been associated with burn-like blister reactions.
Androderm does not have to be removed during sexual intercourse, nor while taking a shower or bath.
Androderm systems should be applied nightly.
Laboratory Tests
Hemoglobin and hematocrit should be checked periodically to detect polycythemia in patients who are receiving androgen therapy.
Liver function, prostate specific antigen, total cholesterol and HDL cholesterol should be checked periodically.
Drug Interactions
Anticoagulants: C-17 substituted derivatives of testosterone, such as methandrostenolone, have been reported to decrease the anticoagulant requirements of patients receiving oral anticoagulants. Patients receiving oral anticoagulants require close monitoring especially when androgens are started or stopped.
Oxyphenbutazone: Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.
Insulin: In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.
Drug/Laboratory Test Interferences
Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased total T_4 serum levels and increased resin uptake of T_3 and T_4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal Data: Testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.
Human Data: There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of drugs did not lead to regression of the tumors in all cases.
Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia.
Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of subclinical or clinical prostate cancer prior to initiation of testosterone replacement therapy, because testosterone therapy may promote the growth of existing subclinical foci of prostate cancer.[2]
In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men.
Pregnancy Category X: (See Contraindications).
Teratogenic Effects: *Androderm* must not be used in women.
Nursing Mothers: *Androderm* must not be used in women.
Pediatric Use: *Androderm* has not been evaluated clinically in males under 15 years of age.

ADVERSE REACTIONS

Adverse Events Associated with Androderm (testosterone transdermal system)
In clinical studies of 122 patients treated with *Androderm*, the most common adverse events reported were skin reactions at the site of system application. Transient mild to moderate erythema was observed at the site of application in the majority of patients at some time during treatment.
The adverse reactions reported by more than 1% of patients are listed below shown in order of decreasing frequency.

Event	Percent of Patients
pruritus at application site	37%
burn-like blister reaction under system	12%
erythema at application site	7%
vesicles at application site	6%
prostate abnormalities	5%
headache	4%
allergic contact dermatitis to the system	4%
burning at application site	3%
induration at application site	3%
depression	3%
rash	2%
gastrointestinal bleeding	2%

The following reactions occurred in less than 1% of patients: fatigue; body pain; pelvic pain; hypertension; peripheral vascular disease; increased appetite; accelerated growth; anxiety; confusion; decreased libido; paresthesia; thinking abnormalities; vertigo; acne; bullae at application site; mechanical irritation at application site; rash at application site; contamination of application site; prostate carcinoma; dysuria; hematuria; impotence; urinary incontinence; urinary tract infection; testicular abnormalities.
Three types of application site reactions occurred: irritation which included mild to moderate erythema, induration or burning; allergic contact dermatitis; and burn-like blister reactions.
Chronic skin irritation caused 5% of patients to discontinue treatment. Mild skin irritation may be ameliorated by treatment of affected skin with over-the-counter topical hydrocortisone cream or topical antihistamine products.
Five patients (4%) developed allergic contact dermatitis after 3 to 8 weeks treatment that required discontinuation. These reactions were characterized by pruritus, erythema, induration and in some instances vesicles or bullae, which recurred with each system application. Rechallenge with components of the system showed ethanol sensitization in 4 patients. One patient's reaction was attributed to testosterone. None of these patients had adverse sequelae related to oral alcohol ingestion or to injectable testosterone use. Older patients may be more prone to develop allergic contact dermatitis.
Fourteen patients (12%) had burn-like blister reactions that involved bullae, epidermal necrosis or the development of ulcerated lesions. These reactions typically occurred once, at a single application site; 5 patients experienced a single recurrence. None withdrew from the clinical trials. These reactions occurred at a rate of approximately 1 in 6,500 system applications (1 in 3,250 treatment days). The majority of these lesions were associated with system application over bony prominences or on parts of the body that may have been subject to prolonged pressure during sleep or sitting (e.g., over the deltoid region of the upper arm, the greater trochanter of the femur, or the ischial tuberosity). The more severe lesions healed over several weeks with scarring in some cases. Such lesions should be treated as burns.
Adverse Events Associated with Injection or Oral Treatments
Skin and Appendages: Hirsutism, male pattern of baldness, seborrhea, and acne.
Endocrine and Urogenital: Gynecomastia and excessive frequency and duration of penile erections. Oligospermia may occur at high dosages (see CLINICAL PHARMACOLOGY).
Fluid and Electrolyte Disturbances: Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.
Gastrointestinal: Nausea, cholestatic jaundice, alterations in liver function tests. Rare instances of hepatocellular neoplasms and peliosis hepatis have occurred (see WARNINGS).
Hematologic: Suppression of clotting factors II, V, VII, and X; bleeding in patients on concomitant anticoagulant therapy and polycythemia.
Nervous System: Increased or decreased libido, headache, anxiety, depression and generalized paresthesia.
Metabolic: Increased serum cholesterol.
Miscellaneous: Rarely, anaphylactoid reactions.

DRUG ABUSE AND DEPENDENCE

Androderm (testosterone transdermal system) is a Schedule III controlled substance under the Anabolic Steroids Control Act.
Oral consumption of the *Androderm* system or the gel contents of the system will not result in clinically significant serum testosterone concentrations in the target organs due to extensive first-pass metabolism.

OVERDOSAGE

There is one report of acute overdosage with testosterone enanthate injection: testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident.

DOSAGE AND ADMINISTRATION

The usual starting dose is two *Androderm* systems applied nightly for 24 hours, providing a total dose of 5 mg/day.
The adhesive side of the *Androderm* system should be applied to a clean, dry area of the skin on the back, abdomen, upper arms, or thighs. Bony prominences, such as the shoulder and hip areas, should be avoided. DO NOT APPLY TO THE SCROTUM. The sites of application should be rotated, with an interval of 7 days between applications to the same site. The area selected should not be oily, damaged, or irritated. (See Table 2.)
The system should be applied immediately after opening the pouch and removing the protective release liner. The system should be pressed firmly in place, making sure there is good contact with the skin, especially around the edges.
To ensure proper dosing, the morning serum testosterone concentration may be measured following system application the previous evening. If the serum concentration is outside the normal range, sampling should be repeated with assurance of proper system adhesion as well as appropriate application time. Confirmed serum concentrations outside the normal range may require increasing the dosing regimen to 3 systems, or decreasing the regimen to 1 system, maintaining nightly application. Because of variability in analytical values among diagnostic laboratories, this laboratory work and any later analyses for assessing the effect of *Androderm* therapy, should be performed at the same laboratory so results can be more easily compared.
Androderm (testosterone transdermal system) therapy for non-virilized patients may be initiated with one system applied nightly.

HOW SUPPLIED

Each system contains 12.2 mg testosterone USP for delivery of 2.5 mg of testosterone per day (see DESCRIPTION).
Cartons of 60 systems NDC 0007-3155-18
Cartons of 30 systems NDC 0007-3155-13
Storage and Disposal
Store at room temperature, 15° to 30°C (59° to 86°F). Apply to skin immediately upon removal from the protective pouch. Do not store outside the pouch provided. Damaged systems should not be used. The drug reservoir may be burst by excessive pressure or heat. Discard systems in household trash in a manner that prevents accidental application or ingestion by children, pets or others.

REFERENCES

1. Mazer NA, et al. Mimicking the circadian pattern of testosterone and metabolite levels with an enhanced transdermal delivery system. In Gurney, Junjinger, Peppas, eds. *Pulsatile Drug Delivery: Current Applications and Future Trends.* Stuttgart: Wiss. Verl.-Ges.; 1993, 73-97.
2. Schroeder FH. Androgens and carcinoma of the prostate. In Neischlag E, Behre HM, eds. *Testosterone Action, Deficiency, Substitution.* Berlin/Heidelberg: Springer-Verlag; 1990, 245-260.

CAUTION: Federal law prohibits dispensing without prescription.
U.S. Patent Nos. 4,849,224, 4,855,294, 4,863,970, 4,983,395, 5,152,997, and 5,164,190.
Manufactured by:
TheraTech, Inc.
Salt Lake City, UT 84108
for **SmithKline Beecham Pharmaceuticals**
Philadelphia, PA
Veterans Administration/Military/PHS—
Testosterone Transdermal System,
2.5 mg, 60's 6505-01-423-4981.
AD:L3

Shown in Product Identification Guide, page 336

Wallace Laboratories—Cont.

Possible side effects include skin rashes, swelling of the salivary glands, and "iodism" (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes stomach upset and diarrhea).

A few people have an allergic reaction with more serious symptoms. These could be fever and joint pains, or swelling of parts of the face and body and at times severe shortness of breath requiring immediate medical attention.

Taking iodide may rarely cause overactivity of the thyroid gland, underactivity of the thyroid gland, or enlargement of the thyroid gland (goiter).

WHAT TO DO IF SIDE EFFECTS OCCUR

If the side effects are severe or if you have an allergic reaction, stop taking potassium iodide. Then, if possible, call a doctor or public health authority for instructions.

HOW SUPPLIED

THYRO-BLOCK® Tablets (Potassium Iodide Tablets, USP) are white, round tablets, one side scored, other side debossed 472 WALLACE, each containing 130 mg potassium iodide. Available in bottles of 14 tablets (NDC 0037-0472-20).

WALLACE LABORATORIES
Division of
CARTER-WALLACE, INC.
Cranbury, New Jersey 08512
IN-0472-03 Rev. 5/94

TUSSI-ORGANIDIN® DM NR* ℞
(*Newly Reformulated) Liquid

TUSSI-ORGANIDIN® DM-S† NR* ℞
(*Newly Reformulated) Liquid
(guaifenesin, dextromethorphan hydrobromide)

Professional Labeling Information and Directions for Use
This product labeled for sale on prescription only.

DESCRIPTION

TUSSI-ORGANIDIN® DM NR* (*Newly Reformulated) Liquid is a clear yellow liquid with a raspberry flavor.

Each 5 mL (1 teaspoon) contains:

Guaifenesin, USP	100 mg
Dextromethorphan Hydrobromide, USP	10 mg

Other ingredients: Citric acid, D&C Yellow No. 10, FD&C Red No. 40, flavor (artificial), glycerin, propylene glycol, purified water, saccharin sodium, sodium benzoate, sorbitol.

Guaifenesin (glyceryl guaiacolate) has the chemical name 3-(2-methoxyphenoxy)-1,2-propanediol. Its molecular formula is $C_{10}H_{14}O_4$, with a molecular weight of 198.21. It is a white, colorless crystalline substance with a slightly bitter aromatic taste. One gram dissolves in 20 mL water at 25°C; freely soluble in ethanol. Guaifenesin is readily absorbed from the GI tract and is rapidly metabolized and excreted in the urine. Guaifenesin has a plasma half-life of one hour. The major urinary metabolite is beta-(2-methoxyphenoxy) lactic acid.

CLINICAL PHARMACOLOGY

TUSSI-ORGANIDIN® DM NR* (*Newly Reformulated) combines the expectorant, guaifenesin and the cough suppressant, dextromethorphan hydrobromide. Guaifenesin is an expectorant the action of which promotes or facilitates the removal of secretions from the respiratory tract. By increasing sputum volume and making sputum less viscous, guaifenesin facilitates expectoration of retained secretions. Dextromethorphan is a synthetic nonopioid cough suppressant, the dextro isomer of the codeine analogue of levorphanol. Dextromethorphan acts centrally to elevate the threshold for coughing, but does not have addictive, analgesic or sedative actions and does not produce respiratory despression with usual doses.

INDICATIONS AND USAGE

Temporarily relieves cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants. Calms the cough control center and relieves coughing. Helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus, drain bronchial tubes, and make coughs more productive.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients. The use of dextromethorphan-containing products is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs).

PRECAUTIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal studies to assess the long-term carcinogenic and mutagenic potential or the effect on fertility in animals or humans of TUSSI-ORGANIDIN DM NR* (*Newly Reformulated) Liquid have not been performed.

Pregnancy.

Teratogenic Effects—Pregnancy Category C: Animal reproduction studies have not been conducted. Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, this product should not be used in pregnant patients, unless in the judgment of the physician, the potential benefits outweigh possible hazards.

Nursing Mothers: It is not known whether guaifenesin or dextromethorphan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when these products are administered to a nursing woman and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Laboratory Test Interactions: Guaifenesin or its metabolites may cause color interference with the VMA (vanillylmandelic acid) test for catechols. It may also falsely elevate the level of urinary 5-HIAA (5-hydroxyindoleacetic acid) in certain serotonin metabolite chemical tests because of color interference.

Drug Interactions: Serious toxicity may result if dextromethorphan is coadministered with monoamine oxidase inhibitors (MAOIs). The use of dextromethorphan hydrobromide may result in additive CNS depressant effects when coadministered with alcohol, antihistamines, psychotropics or other drugs which produce CNS depression.

Information for Patients: Patients should be warned not to use this product if they are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If patients are uncertain whether a prescription drug contains an MAOI, they should be instructed to consult a health professional before taking such a product.

ADVERSE REACTIONS

Guaifenesin is well tolerated and has a wide margin of safety. Nausea and vomiting are the side effecs that occur most commonly. Other reported adverse reactions have included dizziness, headache and rash (including urticaria). Rare drowsiness or mild gastrointestinal disturbances are the only side effects associated with dextromethorphan in clinical use. (see also Drug Interactions)

OVERDOSAGE

Overdosage with guaifenesin is unlikely to produce toxic effects since its toxicity is low. Guaifenesin, when administered by stomach tube to test animals in doses up to 5 grams/kg, produced no signs of toxicity. In severe cases of overdosage, treatment should be aimed at reducing further absorption of the drug. Gastric emptying (emesis and/or gastric lavage) is recommended as soon as possible after ingestion. Overdosage with dextromethorphan may produce excitement and mental confusion. Very high doses may produce respiratory depression. One case of toxic psychosis (hyperactivity, marked visual and auditory hallucinations) after ingestion of a single 300 mg dose of dextromethorphan has been reported.

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age and older: 2 teaspoonfuls (10 mL) every four hours not to exceed 12 teaspoonfuls (60 mL) in 24 hours.

Children 6 years to under 12 years of age: 1 teaspoonful (5 mL) every four hours not to exceed 6 teaspoonfuls (30 mL) in 24 hours.

Children 2 to under 6 years of age: ½ teaspoonful (2.5 mL) every four hours not to exceed 3 teaspoonfuls (15 mL) in 24 hours.

Children 6 mo. to under 2 years of age: A common dosage is ⅛ teaspoonful to ¼ teaspoonful (0.6 mL to 1.25 mL) every 4 hours or ½ teaspoonful (2.5 mL) every 6–8 hours, not to exceed 1.5 teaspoonfuls (7.5 mL) in 24 hours. Individualized dosage should be determined by evaluation of patient.

HOW SUPPLIED

Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL of clear yellow liquid in bottles of one pint (NDC 0037-4714-10) and one gallon (NDC 0037-4714-20), and 4 fl oz (NDC 0037-4714-01) labeled TUSSI-ORGANIDIN® DM-S† NR.*

Storage—Store at controlled room temperature—15°–30°C (59°–86°F). Protect from light. Keep bottle tightly closed.

†TUSSI-ORGANIDIN® DM-S NR* is TUSSI-ORGANIDIN® DM NR* Liquid either in a 4 fl oz unit of use container with a 10 mL graduated oral syringe and fitment or in a 30 mL sample container.

TUSSI-ORGANIDIN® DM NR* (*Newly Reformulated) Liquid is distributed by:
WALLACE LABORATORIES
Division of CARTER-WALLACE, Inc.
Cranbury, NJ 08512
Manufactured by:
Denver Chemical (Puerto Rico) Inc.
Subsidiary of Carter-Wallace, Inc.
Humacao, Puerto Rico 00791
IN-053J8-01 Rev. 7/94

Shown in Product Identification Guide, page 339

VASCOR® ℞
brand of bepridil hydrochloride
Tablets

Marketed jointly by McNeil Pharmaceutical and Wallace Laboratories. See McNeil Pharmaceutical for product information.

VōSoL® ℞
OTIC SOLUTION
(acetic acid otic solution, USP)

VōSoL® HC ℞
OTIC SOLUTION
(hydrocortisone and acetic acid otic solution, USP)

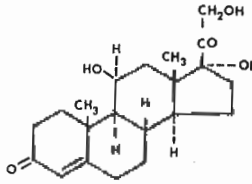
DESCRIPTION

VōSoL (acetic acid otic solution, USP) is a solution of acetic acid (2%), in a propylene glycol vehicle containing propylene glycol diacetate (3%), benzethonium chloride (0.02%), and sodium acetate (0.015%). The empirical formula for acetic acid is CH_3COOH, with a molecular weight of 60.05. The structural formula is:

VōSoL is available as a nonaqueous otic solution buffered at pH 3 for use in the external ear canal.

VōSoL HC (hydrocortisone and acetic acid otic solution, USP) is a solution containing hydrocortisone (1%) and acetic acid (2%), in a propylene glycol vehicle containing propylene glycol diacetate (3%), benzethonium chloride (0.02%), sodium acetate (0.015%) and citric acid (0.05%). The empirical formulas for acetic acid and hydrocortisone are CH_3COOH and $C_{21}H_{30}O_5$, with a molecular weight of 60.05 and 362.46, respectively. The structural formulas are:

Acetic Acid



Chemically, hydrocortisone is:
Pregn-4-ene-3,20-dione,
11,17,21-trihydroxy-(11β)-.

VōSoL HC is available as a nonaqueous otic solution buffered at pH 3 for use in the external ear canal.

CLINICAL PHARMACOLOGY

VōSoL—Acetic acid is antibacterial and antifungal; propylene glycol is hydrophilic and provides a low surface tension; benzethonium chloride is a surface active agent that promotes contact of the solution with tissues.

VōSoL HC—Acetic acid is antibacterial and antifungal; hydrocortisone is anti-inflammatory, antiallergic, and antipruritic; propylene glycol is hydrophilic and provides a low surface tension; benzethonium chloride is a surface active agent that promotes contact of the solution with tissues.

INDICATIONS AND USAGE

VōSoL—For the treatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial.

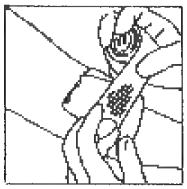
VōSoL HC—For the treatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial, complicated by inflammation.

CONTRAINDICATIONS

VōSoL—Hypersensitivity to VōSoL or any of the ingredients. Perforated tympanic membrane is considered a contraindication to the use of any medication in the external ear canal.

VōSoL HC—Hypersensitivity to VōSoL HC or any of the ingredients; herpes simplex, vaccinia and varicella. Perfo-

Wyeth-Ayerst Laboratories—Cont.



Figures 25 and 26: After the procedure is completed, the incision is closed and bandaged as with insertion. The upper arm should be kept dry for a few days.

Following removal, fertility rates return to levels comparable to those seen in the general population of women using no method of contraception, and a pregnancy may occur at any time.

HINTS

Insertion

—Counselling of the patient on the benefits and side effects of the method prior to insertion will greatly increase patient satisfaction.
—Correct subdermal placement of the capsules will facilitate removal.
—Before insertion, apply the anesthetic just beneath the skin so as to raise the dermis above the underlying tissue.
—Never force the trocar.
—To ensure subdermal placement, the trocar with bevel up should be supported by the index finger and should visibly raise the skin at all times during insertion.
—To avoid damaging the previous implanted capsule, stabilize the capsule with your forefinger and middle finger and advance the trocar alongside the finger tips at an angle of 15 degrees.
—After insertion, make a drawing for the patient's file showing the location of the 6 capsules and describe any variations in placement. This will greatly aid removal.

Removal

—Alternate removal techniques have been developed.
—The removal of the implanted capsules will usually take a little more time than the insertion.
—Before initiating removal, all capsules should be located by palpation. If all six capsules cannot be palpated, they may be localized via ultrasound (7 MHz), X ray, or compression mammography.
—Before removal, apply the anesthetic *under* the capsule ends nearest the original incision site.
—If the removal of some of the capsules proves difficult, interrupt the procedure and have the patient return for another visit. The remaining capsule(s) will be easier to remove after the area is healed.
—It may be appropriate to seek consultation or provide referral for patients in whom initial attempts at capsule removal prove difficult.

Shown in Product Identification Guide, page 340

OMNIPEN® ℞
[*om 'ni-pen*]
(ampicillin)
CAPSULES

DESCRIPTION

Omnipen (ampicillin) is a semisynthetic penicillin derived from the basic penicillin nucleus, 6-amino-penicillanic acid. Ampicillin is designated chemically as (2S,5R,6R)-6-[(R)-2-Amino-2-phenylacetamido] -3,3- dimethyl-7-oxo-4-thia-1-aza -bicyclo [3.2.0] heptane-2-carboxylic acid. The molecular formula for ampicillin is $C_{16}H_{19}N_3O_4S$ with a molecular weight of 349.40.

Omnipen capsules for oral administration contain 250 mg or 500 mg ampicillin anhydrous. The inactive ingredients present are D&C Red 22, D&C Red 28, FD&C Blue 1, gelatin, lactose, methylcellulose, stearic acid, and titanium dioxide.

CLINICAL PHARMACOLOGY

Ampicillin is bactericidal at low concentrations and is clinically effective not only against the gram-positive organisms usually susceptible to penicillin G, but also against a variety of gram-negative organisms. It is stable in the presence of gastric acid and is well absorbed from the gastrointestinal tract. It diffuses readily into most body tissues and fluids; however, penetration into the cerebrospinal fluid and brain occurs only with meningeal inflammation. Ampicillin is excreted largely unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid which inhibits the renal tubular secretion of ampicillin. In blood serum, ampicillin is the least bound of all the penicillins; an average of about 20% of the drug is bound to the plasma proteins as compared to 60 to 90% for the other penicillins. Blood serum levels of approximately 2 mcg/mL are attained within 1 to 2 hours following a 250 mg oral dose given to fasting adults. Detectable amounts persist for about 6 hours.

MICROBIOLOGY

While *in vitro* studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the "**Indications and Usage**" section has not been documented.

Gram-Positive

Alpha- and beta-hemolytic streptococci, *Streptococcus pneumoniae,* staphylococci (non-penicillinase-producing strains), *Bacillus anthracis, Clostridium* sp., *Corynebacterium xerose,* and most strains of enterococci.

Gram-Negative

Hemophilus influenzae, Neisseria gonorrhoeae, Neisseria meningitidis, Proteus mirabilis, and many strains of *Salmonella* (including *S. typhosa*), *Shigella,* and *Escherichia coli.*

NOTE: Ampicillin is inactivated by penicillinase and therefore is ineffective against penicillinase-producing organisms including certain strains of staphylococci, *Pseudomonas aeruginosa, P. vulgaris, Klebsiella pneumoniae, Enterobacter aerogenes,* and some strains of *E. coli.* Ampicillin is not active against Rickettsia, Mycoplasma, and "large viruses" (Miyagawanella).

Testing for Susceptibility

The invading organism should be cultured and its susceptibility demonstrated as a guide to therapy. If the Kirby-Bauer method of disc susceptibility is used, a 10 mcg ampicillin disc should be used to determine the relative *in vitro* susceptibility.

INDICATIONS AND USAGE

Omnipen (ampicillin) Capsules are indicated in the treatment of infections caused by susceptible strains of the following microorganisms:

Infections of the genitourinary tract including gonorrhea—E. coli, P. mirabilis, enterococci, *Shigella, S. typhosa* and other *Salmonella,* and non-penicillinase-producing *N. gonorrhoeae.*

Infections of the respiratory tract—Non-penicillinase-producing *H. influenzae* and staphylococci, and streptococci including *Streptococcus pneumoniae.*

Infections of the gastrointestinal tract—Shigella, S. typhosa and other *Salmonella, E. coli, P. mirabilis,* and enterococci.

Meningitis—N. meningitidis.

Bacteriology studies to determine the causative organisms and their sensitivity to ampicillin should be performed. Therapy may be instituted prior to the results of susceptibility testing.

CONTRAINDICATIONS

The use of this drug is contraindicated in individuals with a history of a previous hypersensitivity reaction to any of the penicillins. Ampicillin is also contraindicated in infections caused by penicillinase-producing organisms.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral administration, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity who experienced severe hypersensitivity reactions when treated with cephalosporins. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

PRECAUTIONS

GENERAL

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms, including fungi. Should superinfection occur, appropriate measures should be taken.

Patients with gonorrhea who also have syphilis should be given additional appropriate parenteral penicillin treatment. Treatment with ampicillin does not preclude the need for surgical procedures, particularly in staphylococcal infections.

INFORMATION FOR THE PATIENT

1. The patient should inform the physician of any history of sensitivity to allergens, including previous hypersensitivity reactions to penicillins and cephalosporins (see "**Warnings**").
2. The patient should discontinue ampicillin and contact the physician immediately if any side effect occurs (see "**Warnings**").
3. Ampicillin should be taken with a full glass (8 oz) of water, one-half hour before or two hours after meals.
4. Diabetic patients should consult with the physician before changing diet or dosage of diabetes medication (see "**Precautions**—DRUG/LABORATORY TEST INTERACTION").

LABORATORY TESTS

In prolonged therapy, and particularly with high dosage regimens, periodic evaluation of the renal, hepatic, and hematopoietic systems is recommended.

In streptococcal infections, therapy must be sufficient to eliminate the organism (10 days minimum); otherwise, the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

Cases of gonococcal infection with a suspected lesion of syphilis should have dark-field examinations ruling out syphilis before receiving ampicillin. Patients who do not have suspected lesions of syphilis and are treated with ampicillin should have a follow-up serologic test for syphilis each month for four months to detect syphilis that may have been masked by treatment for gonorrhea.

DRUG INTERACTIONS

When administered concurrently, the following drugs may interact with ampicillin:

Allopurinol—Increased possibility of skin rash, particularly in hyperuricemic patients, may occur.

Bacteriostatic antibiotics—Chloramphenicol, erythromycins, sulfonamides, or tetracyclines may interfere with the bactericidal effect of penicillins. This has been demonstrated *in vitro;* however, the clinical significance of this interaction is not well-documented.

Oral contraceptives—May be less effective and increased breakthrough bleeding may occur.

Probenecid—May decrease renal tubular secretion of ampicillin resulting in increased blood levels and/or ampicillin toxicity.

DRUG/LABORATORY TEST INTERACTION

After treatment with ampicillin, a false-positive reaction for glucose in the urine may occur with copper sulfate tests (Benedict's solution, Fehling's solution, or Clinitest® tablets) but not with enzyme based tests such as Clinistix® and TesTape®.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evalute carcinogenesis, mutagenesis, or impairment of fertility in males or females.

PREGNANCY: TERATOGENIC EFFECTS

CATEGORY B

Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the fetus due to penicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, penicillin should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs showed that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions, but moderately increased the height and duration of contractions. However, it is not known whether use of these drugs in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

NURSING MOTHERS

Ampicillin-class antibiotics are excreted in milk. Ampicillin use by nursing mothers may lead to sensitization of infants; therefore, a decision should be made whether to discontinue nursing or to discontinue ampicillin, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Penicillins are excreted primarily unchanged by the kidney; therefore, the incompletely developed renal function in neonates and young infants will delay the excretion of penicillin. Administration to neonates and young infants should be limited to the lowest dosage compatible with an effective therapeutic regimen (see "**Dosage and Administration**").

ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

Gastrointestinal: glossitis, stomatitis, nausea, vomiting, enterocolitis, pseudomembranous colitis, and diarrhea. These reactions are usually associated with oral dosage forms of the drug.

Hypersensitivity Reactions: an erythematous, mildly pruritic, maculopapular skin rash has been reported fairly frequently. The rash, which usually does not develop within the first week of therapy, may cover the entire body including the soles, palms, and oral mucosa. The eruption usually disappears in three to seven days. Other hypersensitivity reactions that have been reported are: skin rash, pruritus, urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form of the drug.

NOTE: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy. Serious anaphylactic reactions require emergency measures (see **"Warnings"**).

Liver: A moderate elevation in the serum glutamic-oxaloacetic transaminase (SGOT) has been noted, but the significance of this finding is unknown.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Other adverse reactions that have been reported with the use of ampicillin are laryngeal stridor and high fever. An occasional patient may complain of sore mouth or tongue as with any oral penicillin preparation.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures as required. In patients with renal function impairment, ampicillin-class antibiotics can be removed by hemodialysis but not by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

Adults and children weighing over 20 kg:

For genitourinary- or gastrointestinal-tract infections other than gonorrhea in men and women—the usual dose is 500 mg q.i.d in equally spaced doses (i.e., 500 mg every 6 hours); larger doses may be required for severe or chronic infections.

For the treatment of gonorrhea in both men and women—a single oral dose of 3.5 grams of ampicillin with 1 gram of probenecid administered simultaneously is recommended. Physicians are cautioned to use no less than the above recommended dosage for the treatment of gonorrhea. Follow-up cultures should be obtained from the original site(s) of infection 7 to 14 days after therapy. In women, it is also desirable to obtain culture test-of-cure from both the endocervical and anal canals. Prolonged intensive therapy is needed for complications such as prostatitis and epididymitis.

For respiratory-tract infections—the usual dose is 250 mg q.i.d. in equally spaced doses (i.e., 250 mg every 6 hours).

Children weighing 20 kg or less:

For genitourinary- or gastrointestinal-tract infections—the usual dose is 100 mg/kg/day total, administered q.i.d. in equally divided and spaced doses (i.e., every 6 hours).

For respiratory infections—the usual dose is 50 mg/kg/day total, administered in equally divided and spaced doses three to four times daily (i.e., every 8 to every 6 hours).

Doses for children should not exceed doses recommended for adults.

In all patients, irrespective of age and weight: Larger doses may be required for severe or chronic infections. Although ampicillin is resistant to degradation by gastric acid, it should be administered at least one-half hour before or two hours after meals for maximal absorption. Except for the single-dose regimen for gonorrhea referred to above, therapy should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. In infections caused by hemolytic strains of streptococci, a minimum of 10 days' treatment is recommended to guard against the risk of rheumatic fever or glomerulonephritis (see **"Precautions**—LABORATORY TESTS").

In the treatment of chronic urinary or gastrointestinal infections, frequent bacteriologic and clinical appraisal is necessary during therapy and may be necessary for several months afterwards. Stubborn infections may require treatment for several weeks. Smaller doses than those indicated above should not be used.

HOW SUPPLIED

Omnipen® (ampicillin) Capsules contain 250 mg or 500 mg ampicillin anhydrous and are available as follows:

250 mg, violet and pink capsule marked "WYETH" and "53", in bottles of 500 capsules (NDC 0008-0053-05).

500 mg, violet and pink capsule marked "WYETH" and "309", in bottles of 100 (NDC 0008-0309-03) and 500 capsules (NDC 0008-0309-06).

Keep tightly closed.

Dispense in a tight container.

Store at room temperature, approximately 25° C (77° F).

Shown in Product Identification Guide, page 340 ℞

OMNIPEN® ℞

[*om'nī-pen*]

(ampicillin)

for ORAL SUSPENSION

DESCRIPTION

Omnipen (ampicillin) is a semisynthetic penicillin derived from the basic penicillin nucleus, 6-amino-penicillanic acid. Ampicillin is designated chemically as (2S, 5R, 6R)-6-[(R)-2-Amino -2- phenylacetamido] -3,3- dimethyl -7- oxo -4- thia-1-aza-bicyclo [3.2.0]heptane-2-carboxylic acid. The molecular formula for ampicillin is $C_{16}H_{19}N_3O_4S$ with a molecular weight of 349.40.

Omnipen for oral suspension is a powder which when reconstituted as directed yields a suspension of 125 mg or 250 mg ampicillin per 5 mL. The inactive ingredients present are artificial flavors, colloidal silicon dioxide, methylparaben, propylparaben, sodium benzoate, sodium citrate, sucrose, and water. Each dosage strength of suspension also contains the following:

125 mg per 5 mL—carboxymethylcellulose sodium, FD&C Blue 1, FD&C Red 40, FD&C Yellow 6, and natural flavors; 250 mg per 5 mL—D&C Red 28.

CLINICAL PHARMACOLOGY

Ampicillin is bactericidal at low concentrations and is clinically effective not only against the gram-positive organisms usually susceptible to penicillin G, but also against a variety of gram-negative organisms. It is stable in the presence of gastric acid and is well absorbed from the gastrointestinal tract. It diffuses readily into most body tissues and fluids; however, penetration into the cerebrospinal fluid and brain occurs only with meningeal inflammation.

Ampicillin is excreted largely unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid which inhibits the renal tubular secretion of ampicillin. In blood serum, ampicillin is the least bound of all the penicillins; an average of about 20% of the drug is bound to the plasma proteins as compared to 60 to 90% for the other penicillins. Blood serum levels of approximately 2 mcg/mL are attained within 1 to 2 hours following a 250 mg oral dose given to fasting adults. Detectable amounts persist for about 6 hours.

MICROBIOLOGY

While *in vitro* studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the **"Indications and Usage"** section has not been documented.

Gram-Positive

Alpha- and beta-hemolytic streptococci, *Streptococcus pneumoniae,* staphylococci (non-penicillinase-producing), *Bacillus anthracis, Clostridium* sp., *Corynebacterium xerose,* and most strains of enterococci.

Gram-Negative

Hemophilus influenzae, Neisseria gonorrhoeae, Neisseria meningitidis, Proteus mirabilis, and many strains of Salmonella (including *S. typhosa*), Shigella, and *Escherichia coli.*

NOTE: Ampicillin is inactivated by penicillinase and therefore is ineffective against penicillinase-producing organisms including certain strains of staphylococci, *Pseudomonas aeruginosa, P. vulgaris, Klebsiella pneumoniae, Enterobacter aerogenes,* and some strains of *E. coli.* Ampicillin is not active against Rickettsia, Mycoplasma, and "large viruses" (Miyagawanella).

Testing for Susceptibility

The invading organism should be cultured and its susceptibility demonstrated as a guide to therapy. If the Kirby-Bauer method of disc susceptibility is used, a 10 mcg ampicillin disc should be used to determine the relative *in vitro* susceptibility.

INDICATIONS AND USAGE

Omnipen (ampicillin) for Oral Suspension is indicated in the treatment of infections caused by susceptible strains of the following microorganisms:

Infections of the genitourinary tract including gonorrhea—E. coli, P. mirabilis, enterococci, *Shigella, S. typhosa* and other *Salmonella,* and non-penicillinase-producing *N. gonorrhoeae.*

Infections of the respiratory tract—Non-penicillinase-producing *H. influenzae* and staphylococci, and streptococci including *Streptococcus pneumoniae.*

Infections of the gastrointestinal tract—Shigella, S. typhosa and other *Salmonella, E. coli, P. mirabilis* and enterococci.

Meningitis—N. meningitidis.

Bacteriology studies to determine the causative organisms and their sensitivity to ampicillin should be performed. Therapy may be instituted prior to the results of susceptibility testing.

CONTRAINDICATIONS

The use of this drug is contraindicated in individuals with a history of previous hypersensitivity reaction to any of the penicillins. Ampicillin is also contraindicated in infections caused by penicillinase-producing organisms.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity who experienced severe reactions when treated with cephalosporins. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy instituted.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

PRECAUTIONS

GENERAL

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms, including fungi. Should superinfection occur, appropriate measures should be taken.

Patients with gonorrhea who also have syphilis should be given additional appropriate parenteral penicillin treatment.

Treatment with ampicillin does not preclude the need for surgical procedures, particularly in staphylococcal infections.

INFORMATION FOR THE PATIENT

1. The patient should inform the physician of any history of sensitivity to allergens, including previous hypersensitivity reactions to penicillins and cephalosporins (see **"Warnings"**).
2. The patient should discontinue ampicillin and contact the physician immediately if any side effect occurs (see **"Warnings"**).
3. Ampicillin should be taken with a full glass (8 oz.) of water, one-half hour before or two hours after meals.
4. Diabetic patients should consult with the physician before changing diet or dosage of diabetes medication (see **"Precautions**—DRUG/LABORATORY TEST INTERACTION").

LABORATORY TESTS

In prolonged therapy, and particularly with high dosage regimens, periodic evaluation of the renal, hepatic, and hematopoietic systems is recommended.

In streptococcal infections, therapy must be sufficient to eliminate the organism (10 days minimum); otherwise the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

Cases of gonococcal infection with a suspected lesion of syphilis should have darkfield examination ruling out syphilis before receiving ampicillin. Patients who do not have suspected lesions of syphilis and are treated with ampicillin should have a follow-up serologic test for syphilis each month for four months to detect syphilis that may have been masked by treatment or gonorrhea.

DRUG INTERACTIONS

When administered concurrently, the following drugs may interact with ampicillin:

Allopurinol—Increased possibility of skin rash, particularly in hyperuricemic patients, may occur.

Bacteriostatic antibiotics—Chloramphenicol, erythromycins, sulfonamides, or tetracyclines may interfere with the bactericidal effect of penicillins. This has been demonstrated *in vitro;* however, the clinical significance of this interaction is not well-documented.

Oral contraceptives—May be less effective and increased breakthrough bleeding may occur.

Probenecid—May decrease renal tubular secretion of ampicillin resulting in increased blood levels and/or ampicillin toxicity.

Continued on next page

Wyeth-Ayerst Laboratories—Cont.

DRUG/LABORATORY TEST INTERACTION
After treatment with ampicillin, a false-positive reaction for glucose in the urine may occur with copper sulfate tests (Benedict's solution, Fehling's solution, or Clinitest® tablets) but not with enzyme based tests such as Clinistix® and TesTape®.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Long-term studies in animals have not been performed to evaluate carcinogenesis, mutagenesis, or impairment of fertility in males or females.
PREGNANCY: TERATOGENIC EFFECTS
CATEGORY B
Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the fetus due to penicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, penicillin should be used during pregnancy only if clearly needed.
LABOR AND DELIVERY
Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs showed that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions, but moderately increased the height and duration of contractions. However, it is not known whether use of these drugs in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
NURSING MOTHERS
Ampicillin-class antibiotics are excreted in milk. Ampicillin use by nursing mothers may lead to sensitization of infants; therefore, a decision should be made whether to discontinue nursing or to discontinue ampicillin, taking into account the importance of the drug to the mother.
PEDIATRIC USE
Penicillins are excreted primarily unchanged by the kidney; therefore, the incompletely developed renal function in neonates and young infants will delay the excretion of penicillin. Administration to neonates and young infants should be limited to the lowest dosage compatible with an effective therapeutic regimen (see "**Dosage and Administration**").

ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.
The following adverse reactions have been reported as associated with the use of ampicillin:
Gastrointestinal—glossitis, stomatitis, nausea, vomiting, enterocolitis, pseudomembranous colitis, and diarrhea. These reactions are usually associated with oral-dosage forms of the drug.
Hypersensitivity Reactions —an erythematous, mildly pruritic, maculopapular rash has been reported fairly frequently. The rash, which usually does not develop within the first week of therapy, may cover the entire body, including the soles, palms, and oral mucosa. The eruption usually disappears in three to seven days. Other hypersensitivity reactions that have been reported are: skin rash, pruritis, urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form of the drug.
NOTE: Urticaria, other skin rashes, and serum-sickness-like reactions may be controlled by antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to the ampicillin therapy. Serious anaphylactic reactions require emergency measures (see **WARNINGS**).
Liver—A moderate elevation in serum glutamic-oxaloacetic transaminase (SGOT) has been noted, but the significance of this finding is unknown.
Hemic and Lymphatic Systems—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.
Other adverse reactions that have been reported with the use of ampicillin are laryngeal stridor and high fever. An occasional patient may complain of sore mouth or tongue as with any oral penicillin preparation.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures as required. In patients with renal function impairment, ampicillin-class antibiotics can be removed by hemodialysis but not by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

Adults and children weighing over 20 kg:
For genitourinary- or gastrointestinal-tract infections other than gonorrhea in men and women—the usual dose is 500 mg q.i.d. in equally spaced doses (i.e., 500 mg every 6 hours); larger doses may be required for severe or chronic infections.
For the treatment of gonorrhea in both men and women—a single oral dose of 3.5 grams of ampicillin with 1 gram of probenecid administered simultaneously is recommended. Physicians are cautioned to use no less than the above recommended dosage for the treatment of gonorrhea. Follow-up cultures should be obtained from the original site(s) of infection 7 to 14 days after therapy. In women, it is also desirable to obtain culture test-of-cure from both the endocervical and anal canals. Prolonged intensive therapy is needed for complications such as prostatitis and epididymitis.
For respiratory-tract infections—the usual dose is 250 mg q.i.d. in equally spaced doses (i.e., 250 mg every 6 hours).
Children weighing 20 kg or less:
For genitourinary- or gastrointestinal-tract infections—the usual dose is 100 mg/kg/day total, administered q.i.d. in equally divided and spaced doses (i.e., every 6 hours).
For respiratory infections—the usual dose is 50 mg/kg/day total, administered in equally divided and spaced doses three to four times daily (i.e., every 8 to every 6 hours).
Doses for children should not exceed doses recommended for adults.
In all patients, irrespective of age and weight: Larger doses may be required for severe or chronic infections. Although ampicillin is resistant to degradation by gastric acid, it should be administered at least one-half hour before or two hours after meals for maximal absorption. Except for the single-dose regimen for gonorrhea referred to above, therapy should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. In infections caused by hemolytic strains of streptococci, a minimum of 10 days' treatment is recommended to guard against the risk of rheumatic fever or glomerulonephritis (see "**Precautions**—LABORATORY TESTS").
In the treatment of chronic urinary or gastrointestinal infections, frequent bacteriologic and clinical appraisal is necessary during therapy and may be necessary for several months afterwards. Stubborn infections may require treatment for several weeks. Smaller doses than those indicated above should not be used.

HOW SUPPLIED

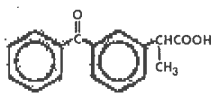
Omnipen® (ampicillin) for Oral Suspension, is available in the following dosage strengths as a powder, which when reconstituted as directed yields a palatable suspension:
125 mg per 5 mL, NDC 0008-0054, white powder in bottles to make 100 mL, 150 mL, or 200 mL of salmon-colored suspension.
250 mg per 5 mL, NDC 0008-0055, white powder in bottles to make 100 mL, 150 mL, or 200 mL of pink suspension.
Store at room temperature [approximately 25° C (77° F)] before reconstitution.
Shake well before using.
Keep tightly closed.
When stored in refrigerator discard unused portion after 14 days, or when stored at room temperature discard unused portion after 7 days (250 mg per 5 mL).
When stored in refrigerator discard unused portion after 14 days (125 mg per 5 mL).

ORUDIS® ℞
[ō″roo′dĭs]
(ketoprofen)
Capsules

ORUVAIL® ℞
[or′ü vāl]
(ketoprofen)
Extended-Release
Capsules

DESCRIPTION

Ketoprofen is a nonsteroidal anti-inflammatory drug. The chemical name for ketoprofen is 2-(3-benzoylphenyl)-propionic acid with the following structural formula:



Its empirical formula is $C_{16}H_{14}O_3$, with a molecular weight of 254.29. It has a pKa of 5.94 in methanol:water (3:1) and an n-octanol:water partition coefficient of 0.97 (buffer pH 7.4).
Ketoprofen is a white or off-white, odorless, nonhygroscopic, fine to granular powder, melting at about 95° C. It is freely soluble in ethanol, chloroform, acetone, ether and soluble in benzene and strong alkali, but practically insoluble in water at 20° C.
Orudis capsules contain 25 mg, 50 mg, or 75 mg of ketoprofen for oral administration. The inactive ingredients present are D&C Yellow 10, FD&C Blue 1, FD&C Yellow 6, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25 mg dosage strength also contains D&C Red 28 and FD&C Red 40.
Each Oruvail 100 mg, 150 mg, or 200 mg capsule contains ketoprofen in the form of hundreds of coated pellets. The dissolution of the pellets is pH dependent with optimum dissolution occurring at pH 6.5–7.5. There is no dissolution at pH 1.
In addition to the active ingredient, each 100 mg, 150 mg, or 200 mg capsule of Oruvail contains the following inactive ingredients: D&C Red 22, D&C Red 28, FD&C Blue 1, ethyl cellulose, gelatin, shellac, silicon dioxide, sodium lauryl sulfate, starch, sucrose, talc, titanium dioxide, and other proprietary ingredients. The 100 and 150 mg capsules also contain D&C Yellow 10 and FD&C Green 3.

CLINICAL PHARMACOLOGY

Ketoprofen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties.
The anti-inflammatory, analgesic, and antipyretic properties of ketoprofen have been demonstrated in classical animal and *in vitro* test systems. In anti-inflammatory models ketoprofen has been shown to have inhibitory effects on prostaglandin and leukotriene synthesis, to have antibradykinin activity, as well as to have lysosomal membrane-stabilizing action. However, its mode of action, like that of other nonsteroidal anti-inflammatory drugs, is not fully understood.

PHARMACODYNAMICS

Ketoprofen is a racemate with only the S enantiomer possessing pharmacological activity. The enantiomers have similar concentration time curves and do not appear to interact with one another.
An analgesic effect-concentration relationship for ketoprofen was established in an oral surgery pain study with Orudis. The effect-site rate constant (k_{e0}) was estimated to be 0.9 $hour^{-1}$ (95% confidence limits: 0 to 2.1), and the concentration (Ce_{50}) of ketoprofen that produced one-half the maximum PID (pain intensity difference) was 0.3 μg/mL (95% confidence limits: 0.1 to 0.5). Thirty-three (33) to 68% of patients had an onset of action (as measured by reporting some pain relief) within 30 minutes following a single oral dose in postoperative pain and dysmenorrhea studies. Pain relief (as measured by remedication) persisted for up to 6 hours in 26 to 72% of patients in these studies.

PHARMACOKINETICS

GENERAL
Orudis and Oruvail capsules both contain ketoprofen. They differ only in their release characteristics. Orudis capsules release drug in the stomach whereas the pellets in Oruvail capsules are designed to resist dissolution in the low pH of gastric fluid but release drug at a controlled rate in the higher pH environment of the small intestine (see "**DESCRIPTION**").
Irrespective of the pattern of release, the systemic availability (F_s) when either oral formulation is compared with IV administration is approximately 90% in humans. For 75 to 200 mg single doses, the area under the curve has been shown to be dose proportional. The figure depicts the plasma time curves associated with both products.
Ketoprofen is >99% bound to plasma proteins, mainly to albumin.
Separate sections follow which delineate differences between Orudis and Oruvail capsules.
ABSORPTION
Orudis capsules—Ketoprofen is rapidly and well-absorbed, with peak plasma levels occurring within 0.5 to 2 hours.
Oruvail capsules—Ketoprofen is also well-absorbed from this dosage form, although an observable increase in plasma levels does not occur until approximately 2 to 3 hours after taking the formulation. Peak plasma levels are usually reached 6 to 7 hours after dosing. (See Figure and Table, below).
When ketoprofen is administered with food, its total bioavailability (AUC) is not altered; however, the rate of absorption from either dosage form is slowed.
Orudis capsules—Food intake reduces C_{max} by approximately one-half and increases the mean time to peak concentration (t_{max}) from 1.2 hours for fasting subjects (range, 0.5 to 3 hours) to 2.0 hours for fed subjects (range, 0.75 to 3 hours). The fluctuation of plasma peaks may also be influenced by circadian changes in the absorption process.
Concomitant administration of magnesium hydroxide and aluminum hydroxide does not interfere with absorption of ketoprofen from Orudis capsules.
Oruvail capsules—Administration of Oruvail with a high-fat meal causes a delay of about 2 hours in reaching the C_{max}; neither the total bioavailability (AUC) nor the C_{max} is al-

PHENERGAN WITH CODEINE

Adults	1 teaspoon (5 mL) every 4 to 6 hours, not to exceed 30.0 mL in 24 hours.
Children 6 years to under 12 years	½ to 1 teaspoon (2.5 to 5 mL) every 4 to 6 hours, not to exceed 30.0 mL in 24 hours.
Children under 6 years (weight: 18 kg or 40 lbs)	¼ to ½ teaspoon (1.25 to 2.5 mL) every 4 to 6 hours, not to exceed 9.0 mL in 24 hours.
Children under 6 years (weight: 16 kg or 35 lbs)	¼ to ½ teaspoon (1.25 to 2.5 mL) every 4 to 6 hours, not to exceed 8.0 mL in 24 hours.
Children under 6 years (weight: 14 kg or 30 lbs)	¼ to ½ teaspoon (1.25 to 2.5 mL) every 4 to 6 hours, not to exceed 7.0 mL in 24 hours.
Children under 6 years (weight: 12 kg or 25 lbs)	¼ to ½ teaspoon (1.25 to 2.5 mL) every 4 to 6 hours, not to exceed 6.0 mL in 24 hours.

Phenergan with codeine is not recommended for children under 2 years of age.

Cardiovascular—Tachycardia, bradycardia, palpitation, faintness, syncope, orthostatic hypotension (common to narcotic analgesics).

Gastrointestinal—Nausea, vomiting, constipation, and biliary tract spasm. Patients with chronic ulcerative colitis may experience increased colonic motility; in patients with acute ulcerative colitis, toxic dilation has been reported.

Genitourinary—Oliguria, urinary retention; antidiuretic effect has been reported (common to narcotic analgesics).

Allergic—Infrequent pruritus, giant urticaria, angioneurotic edema, and laryngeal edema.

Other—Flushing of the face, sweating and pruritus (due to opiate-induced histamine release); weakness.

PROMETHAZINE

Nervous System—Sedation, sleepiness, occasional blurred vision, dryness of mouth, dizziness; rarely confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion (usually in association with parenteral injection or excessive dosage).

Cardiovascular—Increased or decreased blood pressure.

Dermatologic—Rash, rarely photosensitivity.

Hematologic—Rarely leukopenia, thrombocytopenia; agranulocytosis (1 case).

Gastrointestinal—Nausea and vomiting.

DRUG ABUSE AND DEPENDENCE

CONTROLLED SUBSTANCE

Phenergan with codeine is a Schedule V Controlled Substance.

ABUSE

Codeine is known to be subject to abuse; however, the abuse potential of oral codeine appears to be quite low. Even parenteral codeine does not appear to offer the psychic effects sought by addicts to the same degree as heroin or morphine. However, codeine must be administered only under close supervision to patients with a history of drug abuse or dependence.

DEPENDENCE

Psychological dependence, physical dependence, and tolerance are known to occur with codeine.

OVERDOSAGE

CODEINE

Serious overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. The triad of coma, pinpoint pupils, and respiratory depression is strongly suggestive of opiate poisoning. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur. Promethazine is additive to the depressant effects of codeine.

It is difficult to determine what constitutes a standard toxic or lethal dose. However, the lethal oral dose of codeine in an adult is reported to be in the range of 0.5 to 1.0 gram. Infants and children are believed to be relatively more sensitive to opiates on a body-weight basis. Elderly patients are also comparatively intolerant to opiates.

PROMETHAZINE

Signs and symptoms of overdosage with promethazine range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness.

Stimulation may be evident, especially in children and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in children receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.

Atropine-like signs and symptoms—dry mouth, fixed, dilated pupils, flushing, as well as gastrointestinal symptoms, may occur.

TREATMENT

The treatment of overdosage with Phenergan with codeine is essentially symptomatic and supportive. Only in cases of extreme overdosage or individual sensitivity do vital signs including respiration, pulse, blood pressure, temperature, and EKG need to be monitored. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone hydrochloride, may be administered when significant respiratory depression occurs with Phenergan with codeine; any depressant effects of promethazine are not reversed with naloxone. Diazepam may be used to control convulsions. Avoid analeptics, which may cause convulsions. Acidosis and electrolyte losses should be corrected. A rise in temperature or pulmonary complications may signal the need for institution of antibiotic therapy.

Severe hypotension usually responds to the administration of norepinephrine or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since its use in a patient with partial adrenergic blockade may further lower the blood pressure.

Limited experience with dialysis indicates that it is not helpful.

DOSAGE AND ADMINISTRATION

The average effective dose is given in the following table: [See table above.]

HOW SUPPLIED

Phenergan® with codeine is a clear, purple solution supplied as follows:

NDC 0008-0550-02, case of 24 bottles of 4 fl. oz. (118 mL).

NDC 0008-0550-03, bottle of 1 pint (473 mL).

Keep tightly closed—Store at room temperature, between 15° C and 25° C (59° F and 77° F).

Protect from light.

Dispense in light-resistant, glass, tight container.

PHENERGAN® Rx

[fen'er-gan]

with dextromethorphan

(Promethazine Hydrochloride and Dextromethorphan Hydrobromide)

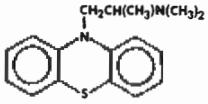
Syrup

DESCRIPTION

Each teaspoon (5 mL) of Phenergan with dextromethorphan contains 6.25 mg promethazine hydrochloride and 15 mg dextromethorphan hydrobromide in a flavored syrup base with a pH between 4.7 and 5.2. Alcohol 7%. The inactive ingredients present are artificial and natural flavors, citric acid, D&C Yellow 10, FD&C Yellow 6, glycerin, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.

Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S \cdot HCl$ and its molecular weight is 320.88.

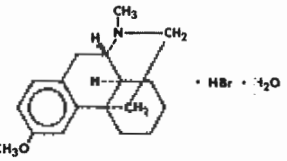
Promethazine hydrochloride, a phenothiazine derivative, is designated chemically as N,N,α-trimethyl-10*H*-phenothiazine-10-ethanamine monohydrochloride with the following structural formula:



Promethazine hydrochloride occurs as a white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is soluble in water and freely soluble in alcohol.

Dextromethorphan hydrobromide is a salt of the methyl ether of the dextrorotatory isomer of levorphanol, a narcotic analgesic. It is chemically named as 3-methoxy-17-methyl-9α, 13α, 14α-morphinan hydrobromide monohydrate with the following structural formula:

[See structure at top of next column.]



Dextromethorphan hydrobromide monohydrate occurs as white crystals, is sparingly soluble in water, and is freely soluble in alcohol. The empirical formula is $C_{18}H_{25}NO \cdot HBr \cdot H_2O$, and the molecular weight of the monohydrate is 370.33. Dextromethorphan HBr monohydrate is dextrorotatory with a specific rotation of +27.6 degrees in water (20 degrees C, sodium D-line).

CLINICAL PHARMACOLOGY

PROMETHAZINE

Promethazine is a phenothiazine derivative which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopaminergic (CNS) action.

Promethazine is an H_1 receptor blocking agent. In addition to its antihistaminic action, it provides clinically useful sedative and antiemetic effects. In therapeutic dosages, promethazine produces no significant effects on the cardiovascular system.

Promethazine is well absorbed from the gastrointestinal tract. Clinical effects are apparent within 20 minutes after oral administration and generally last four to six hours, although they may persist as long as 12 hours. Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demethylpromethazine are the predominant metabolites appearing in the urine.

DEXTROMETHORPHAN

Dextromethorphan is an antitussive agent and, unlike the isomeric levorphanol, it has no analgesic or addictive properties.

The drug acts centrally and elevates the threshold for coughing. It is about equal to codeine in depressing the cough reflex. In therapeutic dosage dextromethorphan does not inhibit ciliary activity.

Dextromethorphan is rapidly absorbed from the gastrointestinal tract and exerts its effect in 15 to 30 minutes. The duration of action after oral administration is approximately three to six hours. Dextromethorphan is metabolized primarily by liver enzymes undergoing O-demethylation, N-demethylation, and partial conjugation with glucuronic acid and sulfate. In humans, (+)-3-hydroxy-N-methylmorphinan, (+)-3-hydroxymorphinan, and traces of unmetabolized drug were found in urine after oral administration.

INDICATIONS AND USAGE

Phenergan with dextromethorphan is indicated for the temporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold.

CONTRAINDICATIONS

Promethazine is contraindicated in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines.

Antihistamines are contraindicated for use in the treatment of lower respiratory tract symptoms, including asthma.

Dextromethorphan should not be used in patients receiving a monoamine oxidase inhibitor (MAOI).

WARNINGS

PROMETHAZINE

Promethazine may cause marked drowsiness. Ambulatory patients should be cautioned against such activities as driving or operating dangerous machinery until it is known that they do not become drowsy or dizzy from promethazine therapy.

The sedative action of promethazine hydrochloride is additive to the sedative effects of central nervous system depressants; therefore, agents such as alcohol, narcotic analgesics, sedatives, hypnotics, and tranquilizers should either be eliminated or given in reduced dosage in the presence of promethazine hydrochloride. When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half, and the dose of analgesic depressants, such as morphine or meperidine, should be reduced by one-quarter to one-half.

Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or when giving in combination with narcotics or local anesthetics which may also affect seizure threshold.

Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea.

Antihistamines should be used with caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder obstruction due to

Continued on next page

Wyeth-Ayerst Laboratories—Cont.

symptomatic prostatic hypertrophy and narrowing of the bladder neck.
Administration of promethazine has been associated with reported cholestatic jaundice.
DEXTROMETHORPHAN
Administration of dextromethorphan may be accompanied by histamine release and should be used with caution in atopic children.

PRECAUTIONS

Animal reproduction studies have not been conducted with the drug combination—promethazine and dextromethorphan. It is not known whether this drug combination can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phenergan with dextromethorphan should be given to a pregnant woman only if clearly needed.
GENERAL
Promethazine should be used cautiously in persons with cardiovascular disease or with impairment of liver function.
Dextromethorphan should be used with caution in sedated patients, in the debilitated, and in patients confined to the supine position.
INFORMATION FOR PATIENTS
Phenergan with dextromethorphan may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery.
Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy from Phenergan with dextromethorphan therapy. Children should be supervised to avoid potential harm in bike riding or in other hazardous activities.
The concomitant use of alcohol or other central nervous system depressants, including narcotic analgesics, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced.
Patients should be advised to report any involuntary muscle movements or unusual sensitivity to sunlight.
DRUG INTERACTIONS
The sedative action of promethazine is additive to the sedative effects of other central nervous system depressants, including alcohol, narcotic analgesics, sedatives, hypnotics, tricyclic antidepressants, and tranquilizers; therefore, these agents should be avoided or administered in reduced dosage to patients receiving promethazine.
DRUG/LABORATORY TEST INTERACTIONS
The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:
Pregnancy Tests
Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.
Glucose Tolerance Test
An increase in blood glucose has been reported in patients receiving promethazine.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine or of dextromethorphan. There are no animal or human data concerning the carcinogenicity, mutagenicity, or impairment of fertility with these drugs. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.
PREGNANCY
Teratogenic Effects —Pregnancy Category C
Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg of promethazine. These doses are 8.3 and 16.7 times the maximum recommended total daily dose for a 50-kg subject. Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines, including promethazine, have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of promethazine in pregnant women.
Phenergan with dextromethorphan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nonteratogenic Effects
Promethazine taken within two weeks of delivery may inhibit platelet aggregation in the newborn.
LABOR AND DELIVERY
See "Nonteratogenic Effects."
NURSING MOTHERS
It is not known whether promethazine or dextromethorphan is excreted in human milk. Caution should be exercised when Phenergan with dextromethorphan is administered to a nursing woman.
PEDIATRIC USE
This product should not be used in children under 2 years of age because safety for that use has not been established.

ADVERSE REACTIONS

PROMETHAZINE
Nervous System —Sedation, sleepiness, occasional blurred vision, dryness of mouth, dizziness; rarely confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion (usually in association with parenteral injection or excessive dosage).
Cardiovascular —Increased or decreased blood pressure.
Dermatologic —Rash, rarely photosensitivity.
Hematologic —Rarely leukopenia, thrombocytopenia; agranulocytosis (1 case).
Gastrointestinal —Nausea and vomiting.
DEXTROMETHORPHAN
Dextromethorphan hydrobromide occasionally causes slight drowsiness, dizziness, and gastrointestinal disturbances.

DRUG ABUSE AND DEPENDENCE

According to the WHO Expert Committee on Drug Dependence, dextromethorphan could produce very slight psychic dependence but no physical dependence.

OVERDOSAGE

PROMETHAZINE
Signs and symptoms of overdosage with promethazine range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness.
Stimulation may be evident, especially in children and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in children receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.
Atropine-like signs and symptoms—dry mouth, fixed, dilated pupils, flushing, as well as gastrointestinal symptoms, may occur.
DEXTROMETHORPHAN
Dextromethorphan may produce central excitement and mental confusion. Very high doses may produce respiratory depression. One case of toxic psychosis (hyperactivity, marked visual and auditory hallucinations) after ingestion of a single dose of 20 tablets (300 mg) of dextromethorphan has been reported.
TREATMENT
Treatment of overdosage with Phenergan with dextromethorphan is essentially symptomatic and supportive. Only in cases of extreme overdosage or individual sensitivity do vital signs including respiration, pulse, blood pressure, temperature, and EKG need to be monitored. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected.
The antidotal efficacy of narcotic antagonists to dextromethorphan has not been established; note that any of the depressant effects of promethazine are not reversed by naloxone. Avoid analeptics, which may cause convulsions.
Severe hypotension usually responds to the administration of norepinephrine or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since its use in a patient with partial adrenergic blockade may further lower the blood pressure.
Limited experience with dialysis indicates that it is not helpful.

DOSAGE AND ADMINISTRATION

The average effective dose for adults is one teaspoon (5 mL) every 4 to 6 hours, not to exceed 30.0 mL in 24 hours. For children 6 years to under 12 years of age, the dose is one-half to one teaspoon (2.5 to 5.0 mL) every 4 to 6 hours, not to exceed 20.0 mL in 24 hours. For children 2 years to under 6 years of age, the dose is one-quarter to one-half teaspoon (1.25 to 2.5 mL) every 4 to 6 hours, not to exceed 10.0 mL in 24 hours.
Phenergan with dextromethorphan is not recommended for children under 2 years of age.

HOW SUPPLIED

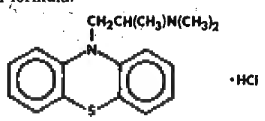
Phenergan® with dextromethorphan (Promethazine Hydrochloride and Dextromethorphan Hydrobromide) Syrup is a clear, yellow solution supplied as follows:
NDC 0008-0548-02, case of 24 bottles of 4 fl. oz. (118 mL).
NDC 0008-0548-03, bottle of 1 pint (473 mL).
Keep bottles tightly closed and store at room temperature between 15° and 25°C (59° and 77°F).
Protect from light.
Dispense in light-resistant, glass, tight containers.

PHENERGAN® VC

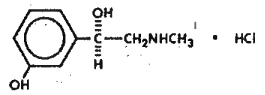
[fen 'er-gan]
(Promethazine Hydrochloride and Phenylephrine Hydrochloride) Syrup

DESCRIPTION

Each teaspoon (5 mL) of Phenergan VC contains 6.25 mg promethazine hydrochloride and 5 mg phenylephrine hydrochloride in a flavored syrup base with a pH between 4.7 and 5.2. Alcohol 7%. The inactive ingredients present are artificial and natural flavors, citric acid, FD&C Yellow 6, glycerin, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.
Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S \cdot HCl$ and its molecular weight is 320.88.
Promethazine hydrochloride, a phenothiazine derivative, is designated chemically as N,N,α-trimethyl-10*H*-phenothiazine-10-ethanamine monohydrochloride with the following structural formula:



Promethazine hydrochloride occurs as white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is soluble in water and freely soluble in alcohol.
Phenylephrine hydrochloride is a sympathomimetic amine salt. It may be chemically named as 3-hydroxy-α-[(methylamino)methyl]-benzenemethanol hydrochloride and has the following chemical formula:



Phenylephrine hydrochloride occurs as white or nearly white crystals, having a bitter taste. It is freely soluble in water and alcohol, with a molecular weight of 203.67. The empirical formula is $C_9H_{13}NO_2 \cdot HCl$, and the stereochemistry is R-isomer as indicated in the structure; Specific Rotation—between −42° and −47.5°.
Phenylephrine hydrochloride is subject to oxidation and must be protected from light and air.

CLINICAL PHARMACOLOGY

PROMETHAZINE
Promethazine is a phenothiazine derivative which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopaminergic (CNS) action.
Promethazine is an H_1 receptor blocking agent. In addition to its antihistaminic action, it provides clinically useful sedative and antiemetic effects. In therapeutic dosages, promethazine produces no significant effects on the cardiovascular system.
Promethazine is well absorbed from the gastrointestinal tract. Clinical effects are apparent within 20 minutes after oral administration and generally last four to six hours, although they may persist as long as 12 hours. Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demethylpromethazine are the predominant metabolites appearing in the urine.
PHENYLEPHRINE
Phenylephrine is a potent postsynaptic α-receptor agonist with little effect on β receptors of the heart. Phenylephrine has no effect on β-adrenergic receptors of the bronchi or peripheral blood vessels. A direct action at receptors accounts for the greater part of its effects, only a small part being due to its ability to release norepinephrine.
Therapeutic doses of phenylephrine mainly cause vasoconstriction. Phenylephrine increases resistance and, to a lesser extent, decreases capacitance of blood vessels. Total peripheral resistance is increased, resulting in increased systolic and diastolic blood pressure. Pulmonary arterial pressure is usually increased, and renal blood flow is usually decreased.
Local vasoconstriction and hemostasis occur following topical application or infiltration of phenylephrine into tissues.
The main effect of phenylephrine on the heart is bradycardia; it produces a positive inotropic effect on the myocardium in doses greater than those usually used therapeutically. Rarely, the drug may increase the irritability of the heart, causing arrhythmias. Cardiac output is decreased slightly. Phenylephrine increases the work of the heart by increasing peripheral arterial resistance.
Phenylephrine has a mild central stimulant effect.
Following oral administration or topical application of phenylephrine to the mucosa, constriction of blood vessels in the