PDR®
42
EDITION
1988

PHYSICIANS' DESK REFERENCE®

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Boots—Cont.

nal irritation, undiluted large single doses (more than a tablespoonful or 15 ml) of TWIN-K-Cl are to be avoided.
To minimize gastrointestinal irritation, it is recommended that TWIN-K-Cl be taken with meals or diluted with water or fruit juice. A tablespoonful (15 ml) in 8 ounces of water is approximately isotonic. More than a single tablespoonful should not be taken without prior dilution.
Deviations from this schedule may be indicated, since no average total daily dose can be defined, but must be governed by close observation for clinical effects.

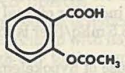
HOW SUPPLIED
Bottles of 1 pint (16 fl. oz.)
NDC 0524-0022-16
Caution: Federal law prohibits dispensing without prescription.

Manufactured and Distributed by
Boots Pharmaceuticals, Inc.
Shreveport, Louisiana 71106 U.S.A.

Rev. 11/83 0022-02

ZORprin® ℞
(aspirin)
(Zero-Order Release)

DESCRIPTION
Each capsule-shaped tablet of ZORPRIN contains 800 mg of aspirin, formulated in a special matrix to control the release of aspirin after ingestion. The in vitro release of aspirin from the tablet matrix is linear and independent of the concentration of the drug.
The structural formula of aspirin is



CLINICAL PHARMACOLOGY
Aspirin, as contained in ZORPRIN, is a salicylate that has demonstrated anti-inflammatory and analgesic activity. Its mode of action as an anti-inflammatory and analgesic agent may be due to the inhibition of synthesis of prostaglandins, although its exact mode of action is not known.
ZORPRIN dissolution is pH dependent. In vitro studies have shown very little aspirin to be released in acidic solutions; whereas, ZORPRIN releases the majority of its aspirin (90%) in a zero-order mode at a neutral to alkaline pH. It is this pH dependence of ZORPRIN that reduces direct contact between aspirin and the gastric mucosa, resulting in a reduction of its gastrointestinal side-effect potential.
Bioavailability data for ZORPRIN have confirmed that plasma levels of salicylic acid and acetylsalicylic acid can be measured 24 hours after a single oral dose. This substantiates a twice daily dose regimen. Multiple dose bioavailability studies showed similar steady-state salicylate levels for ZORPRIN as for conventional release aspirin using the same total daily dose. Long-term monitoring of salicylate levels showed no signs of accumulation once steady-state levels were reached (4–6 days).
Studies of in vivo prostaglandin levels (PGE2) have shown ZORPRIN plasma levels of salicylic acid and acetylsalicylic acid to reduce PGE2 levels 14 hours after a single oral 800 mg dose while an equivalent dose of aspirin produced a reduction of PGE2 levels only through six hours. ZORPRIN's effect on other prostaglandins than PGE2 has not been determined.
Salicylates are excreted mainly by the kidney, and from studies in humans it appears that salicylate is excreted in the urine as free salicylic acid (10%); salicyluric acid (75%); salicylic phenolic (10%); acyl glucuronides (5%) and gentisic acid (<1%).

INDICATIONS & USAGE
ZORPRIN is indicated for the treatment of rheumatoid arthritis and osteoarthritis. The safety and efficacy of ZORPRIN have not been established in those rheumatoid arthritic patients who are designated by the American Rheumatism Association as Functional Class IV (incapacitated, largely or wholly bedridden, or confined to wheelchair, little or no self-care).
In patients treated with ZORPRIN for rheumatoid arthritis and osteoarthritis, the anti-inflammatory action of ZORPRIN has been shown by reduction in pain, morning stiffness and disease activity as assessed by both the investigators and patients.
In clinical studies in patients with rheumatoid arthritis and osteoarthritis, ZORPRIN has been shown to be comparable to conventional release aspirin in controlling the aforementioned signs and symptoms of disease activity and to be associated with a statistically significant reduction in the milder gastrointestinal side effects (see ADVERSE REACTIONS). ZORPRIN may be well tolerated in some patients who have had gastrointestinal side effects with conventional release aspirin, but these patients when treated with ZORPRIN should be carefully followed for signs and symptoms of gastrointestinal bleeding and ulceration.
Since there have been no controlled trials to demonstrate whether or not there is any beneficial effect or harmful interaction with the use of ZORPRIN in conjunction with other nonsteroidal anti-inflammatory agents (NSAI), the combination cannot be recommended (see **Drug Interactions**).
Because of its relatively long onset of action, ZORPRIN is not recommended for antipyresis or for short-term analgesia.

CONTRAINDICATIONS
ZORPRIN should not be used in patients known to be hypersensitive to salicylates or in individuals with the syndrome of nasal polyps, angioedema, bronchospastic reactivity to aspirin, renal or hepatic insufficiency, hypoprothrombinemia or other bleeding disorders. ZORPRIN is not recommended for children under 12 years of age; it is contraindicated in all children with fever accompanied by dehydration.

WARNINGS
ZORPRIN should be used with caution when anticoagulants are prescribed concurrently, since aspirin may depress platelet aggregation and increase bleeding time. Large doses of salicylates may have hypoglycemic action and enhance the effect of the oral hypoglycemics; concomitant use therefore is not recommended. However, if such use is necessary, dosage of the hypoglycemic agent must be reduced. The hypoglycemic action of the salicylates may also necessitate adjustment of the insulin requirements of diabetics.
While salicylates in large doses have a uricosuric effect, smaller amounts may reduce urate excretion and increase serum uric acid.
Although ZORPRIN is not indicated for the treatment of chicken pox or flu, nor for use in children under the age of twelve, children and teenagers, before using this product for or while suffering from chicken pox, influenza or flu symptoms, should consult a doctor. Aspirin may increase the risk of developing Reye's Syndrome, a rare but serious illness.
USE IN PREGNANCY: Aspirin can harm the fetus when administered to pregnant women. Aspirin interferes with maternal and infant hemostasis and may lengthen the duration of pregnancy and parturition. Aspirin has produced teratogenic effects and increases the incidence of stillbirths and neonatal deaths in animals.
If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
Aspirin should not be taken during the last 3 months of pregnancy.

PRECAUTIONS
Appropriate precautions should be taken in prescribing ZORPRIN for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. As with all salicylate drugs, caution should be exercised in prescribing ZORPRIN for those patients with bleeding tendencies or those on anticoagulants.
In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ZORPRIN is made a part of the treatment program.
Patients receiving large doses of aspirin and/or prolonged therapy may develop mild salicylate intoxication (salicylism) that may be reversed by dosage reduction.
Salicylates can produce changes in thyroid function tests.
Salicylates should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, Vitamin K deficiency and in those undergoing surgery.
Since aspirin release from ZORPRIN® (aspirin) is pH dependent, it may change in those conditions where the gastric pH has been increased as a result of antacids, gastric secretion inhibitors or surgical procedures.
Drug Interactions: (See **WARNINGS**) Aspirin may interfere with some anticoagulant and antidiabetic drugs. Drugs which lower serum uric acid by increasing uric acid excretion (uricosurics) may be antagonized by the concomitant use of aspirin, particularly in doses less than 2.0 grams/day. Nonsteroidal anti-inflammatory drugs may be competitively displaced from their albumin binding sites by aspirin. This effect may negate the clinical efficacy of both drugs. Also, the gastrointestinal inflammatory potential of nonsteroidal anti-inflammatory drugs may be potentiated by aspirin. The combination of alcohol and aspirin may increase the risk of gastrointestinal bleeding.
Aspirin may enhance the activity of methotrexate and increase its toxicity.
Sodium excretion produced by spironolactone may be decreased in the presence of salicylates. Concomitant administration of other anti-inflammatory drugs may increase the risk of gastrointestinal ulceration. Urinary alkalinizers decrease aspirin's effectiveness by increasing the rate of salicylate renal excretion. Phenobarbital decreases aspirin effectiveness by enzyme induction.
Pregnancy Category D. See **WARNINGS** Section.
Nursing Mothers: Salicylates have been detected in the breast milk of nursing mothers. Because of the potential for serious adverse reactions in nursing infants from aspirin, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the benefit of the drug to the mother.

ADVERSE REACTIONS
Hematologic: Aspirin interferes with hemostasis. Patients with a history of blood coagulation defects or receiving anticoagulant drugs or with severe anemia should avoid ZORPRIN. Aspirin used chronically may cause a persistent iron deficiency anemia.
Gastrointestinal: Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from ZORPRIN is designed to occur in the small intestine over a period of time. This has resulted in fewer symptomatic gastrointestinal side effects.
Allergic: Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. Fatal anaphylactic shock, while not common, has been reported.
Respiratory: Aspirin intolerance, manifested by exacerbation of bronchospasm and rhinitis, may occur in patients with a history of nasal polyps, asthma, or rhinitis. The mechanism of this intolerance is unknown but may be the result of aspirin-induced shunting of prostaglandin synthesis to the lipoxygenase pathway and the liberation of leukotrienes, e.g., slow-reacting substance of anaphylaxis.
Dermatologic: Hives, rashes, and angioedema may occur, especially in patients suffering from chronic urticaria.
Central Nervous System: Taken in overdoses, aspirin provides stimulation which may be manifested by tinnitus. Following initial stimulation, depression of the central nervous system may be noted.
Renal: Aspirin rarely may aggravate chronic kidney disease.
Hepatic: High doses of aspirin have been reported to produce reversible hepatic dysfunction.

OVERDOSAGE
Overdosage, if it occurs would produce the usual symptoms of salicylism: tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting or diarrhea. Plasma salicylate levels in adults may range from 50 to 80 mg/dl in the mildly intoxicated patient to 110 to 160* mg/dl in the severely intoxicated patient. An arterial blood pH of 7.1 may indicate serious poisoning. The clearance of salicylates in children is much slower than adults and this should receive due consideration when aspirin overdosages occur in infants; salicylate half-lives of 30 hours have been reported in infants 4–8 months old. Treatment for mild intoxication should include emptying the stomach with an emetic, or gastric lavage with 5% sodium bicarbonate. Individuals suffering from severe intoxication should, in addition, have forced diuresis by intravenous infusions of sodium bicarbonate and dextrose or sodium lactate. In extreme cases, hemodialysis or peritoneal dialysis may be required.
(*A plasma salicylate level of 160 mg/dl in an adult is usually considered lethal.)

DOSAGE & ADMINISTRATION
In order to achieve a zero-order release, the tablets of ZORPRIN should be swallowed intact.
Breaking the tablets or disrupting the structure will alter the release profile of the drug.
It is recommended that ZORPRIN be taken with sufficient quantities of fluids (8 oz. or more).
Adult Dosage: For mild to moderate pain associated with rheumatoid arthritis and osteoarthritis, the recommended initial dose of ZORPRIN is 1600 mg (2-800 mg tablets) twice a day. Because of ZORPRIN's prolonged release of aspirin into the bloodstream, the tablets may be taken as a b.i.d. dose. Further adjustment of the dosage should be determined by the physician, based upon the patient's response and needs. Since it will take 4–6 days to reach steady-state levels of salicylic acid with ZORPRIN, it is recommended that dosages be given for at least one week before further adjustment. In general, patients with rheumatoid arthritis seem to require higher doses of ZORPRIN than do patients with osteoarthritis.
ZORPRIN is not recommended for children below the age of 12.

HOW SUPPLIED
ZORPRIN Tablets 800 mg; plain, white capsule-shaped tablets.
Bottles of 100 Tablets—NDC 0524-0057-01
Caution: Federal law prohibits dispensing without prescription.

U.S. Patent No. 4,308,251

BOOTS PHARMACEUTICALS, INC.
Shreveport, Louisiana 71106 USA

0057-08

Rev. 3-87

Shown in Product Identification Section, page 406

Boyle & Company
1030 SO. ARROYO PARKWAY
PASADENA, CA 91105

CITRA® FORTE SYRUP
Oral Solution

℞

PRODUCT OVERVIEW

KEY FACTS
Citra Forte Syrup is a unique combination of two antihistamines and a proven antitussive in a sodium free, pleasant tasting vehicle.

MAJOR USES
Citra Forte has been used successfully for many years to provide cough suppressant action where a narcotic antitussive is indicated or where the cough is caused by a histamine response.

SAFETY INFORMATION
Citra Forte is contraindicated in patients with allergies to the formula ingredients and should be used with caution in patients with hypertension, cardiac disease, diabetes or hyperthyroidism.

PRESCRIBING INFORMATION

CITRA® FORTE SYRUP
Oral Solution

℞

COMPOSITION

	ea. 5 ml
Hydrocodone Bitartrate (Warning: May be habit forming)	5 mg
Pheniramine Maleate	2.5 mg
Pyrilamine Maleate	3.33 mg

Alcohol 2% in a pleasant flavored syrup base with Ascorbic Acid 30 mg and Potassium Citrate 150 mg.

ACTION AND USES
CITRA FORTE SYRUP: Antitussive, Expectorant, Antihistaminic, Provides effective cough suppressant action sodium free. Two antihistamines to help control allergic reactions.

ADMINISTRATION AND DOSAGE
CITRA FORTE SYRUP: Usual Adult Dose.—One or two teaspoonfuls every 3 or 4 hours. *Children* (6-12)—one-half adult dosage. *Children under 6 years*—according to standard method of calculation.

PRECAUTIONS
Patients should be advised to avoid using machinery or driving until response to antihistamines is established. Use with caution in patients with idiosyncrasies to formula ingredients. CITRA FORTE should be used with caution in patients with hypertension, cardiac disease, diabetes or hyperthyroidism.

HOW SUPPLIED
CITRA FORTE SYRUP in pints and gallons.
Caution: Federal (USA) law prohibits dispensing without prescription.

TRIVA® DOUCHE POWDER
FOR VAGINAL USE ONLY

PRODUCT OVERVIEW

KEY FACTS
Triva powder effectively treats Monilial and Trichomonal vaginal infections as well as non-specific Vulvovaginitis. Treatment is antiseptic as well as symptomatic.

MAJOR USES
When used as directed as a douche, chronic, stubborn cases of Monilia and Trichomonas occurring separately or together can be eradicated along with symptoms.

SAFETY INFORMATION
Occasionally irritation occurs at the onset of treatment. Triva is contraindicated in patients with allergies to the formula ingredients.

PRESCRIBING INFORMATION

TRIVA® DOUCHE POWDER
FOR VAGINAL USE ONLY

COMPOSITION
Triva Douche Powder contains (per 3 g packet):

Oxyquinoline Benzoate	60 mg (2%)
Alkyl Aryl Sulfonate	1.05 g (35%)
Disodium Edetate	10 mg (0.33%)
Sodium Sulfate	1.59 g (52.5%)
Lactose (dispersant)	290 mg (9.67%)

ACTION AND USES
TRIVA DOUCHE POWDER effectively treats Monilial and Trichomonal as well as Non-specific Vulvovaginitis. Chronic, stubborn cases as well as Monilia and Trichomonas occurring together can be successfully treated. Organisms are eradicated along with symptoms. Vaginal flora and pH return to normal spontaneously. Trichomonacidal, bactericidal, detergent and chelating agents are provided for a safe, simple, patient-administered treatment without need for restraints on patient's activities. Flushing and detergent action of the douche quickly destroys the infection and stops the symptoms.
Effectiveness of TRIVA DOUCHE POWDER has been demonstrated by clinical tests. Both diagnosis and cure were established by the use of special Papanicolaou smear and Sabouraud culture.

ADMINISTRATION AND DOSAGE
TRIVA DOUCHE POWDER (individual packet dissolved in 1 qt water) is effective in most cases of Monilial, Trichomonal and Non-specific Vulvovaginitis. It provides rapid relief from symptoms. Particularly useful in pre- and post-operative and post-partum care. May be used adjunctively with oral treatment for Trichomonas.
TRIVA DOUCHE POWDER, sig, douche (1 packet in 1 qt water) morning and night for 12 days.
IMPORTANT: During menstruation, continue treatment as instructed.

PRECAUTIONS
Occasionally, irritation occurs at the onset of treatment. In such cases it is recommended that the douche be prescribed in one-half or less than usual strength for a day or two, then treatment resumed as directed.

SIDE EFFECTS
None.

CONTRAINDICATIONS
Allergy or hypersensitivity to any ingredient.

HOW SUPPLIED
TRIVA DOUCHE POWDER—24 individual 3 G packets.

Braintree Laboratories, Inc.
285 WASHINGTON STREET
BRAINTREE, MA 02184

GoLYTELY®
[go-līt'lē]
PEG-3350 and Electrolytes For Oral Solution

℞

DESCRIPTION
A white powder for reconstitution containing 236 g polyethylene glycol 3350, 22.74 g sodium sulfate, 6.74 g sodium bicarbonate, 5.86 g sodium chloride, and 2.97 g potassium chloride. When dissolved in water to a volume of 4 liters, GoLYTELY is an isosmotic solution having a mildly salty taste. GoLYTELY is administered orally or via nasogastric tube.

CLINICAL PHARMACOLOGY
GoLYTELY induces a diarrhea which rapidly cleanses the bowel, usually within four hours. The osmotic activity of polyethylene glycol 3350 and the electrolyte concentration result in virtually no net absorption or excretion of ions or water. Accordingly, large volumes may be administered without significant changes in fluid or electrolyte balance.

INDICATIONS AND USAGE
GoLYTELY is indicated for bowel cleansing prior to colonoscopy and barium enema x-ray examination.

CONTRAINDICATIONS
GoLYTELY is contraindicated in patients with gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, toxic megacolon or ileus.

WARNINGS
No additional ingredients, e.g. flavorings, should be added to the solution. GoLYTELY should be used with caution in patients with severe ulcerative colitis.

PRECAUTIONS
General: Patients with impaired gag reflex, unconscious or semiconscious patients, and patients prone to regurgitation or aspiration, should be observed during the administration of GoLYTELY, especially if it is administered via nasogastric tube. If a patient experiences severe bloating, distention or abdominal pain, administration should be slowed or temporarily discontinued until the symptoms abate. If gastrointestinal obstruction or perforation is suspected, appropriate studies should be performed to rule out these conditions before administration of GoLYTELY.
Information for patients: GoLYTELY produces a watery stool which cleanses the bowel before examination. Prepare the solution according to the instructions on the bottle. It is more palatable if chilled. For best results, no solid food should be consumed during the 3 to 4 hour period before drinking the solution, but in no case should solid foods be eaten within 2 hours of taking GoLYTELY.
Drink 240 ml (8 oz.) every 10 minutes. Rapid drinking of each portion is better than drinking small amounts continuously. The first bowel movement should occur approximately one hour after the start of GoLYTELY administration. You may experience some abdominal bloating and distention before the bowels start to move. If severe discomfort or distention occur, stop drinking temporarily or drink each portion at longer intervals until these symptoms disappear. Continue drinking until the watery stool is clear and free of solid matter. This usually requires at least 3 liters and it is best to drink all of the solution. Any unused portion should be discarded.
Drug Interactions: Oral medication administered within one hour of the start of administration of GoLYTELY may be flushed from the gastrointestinal tract and not absorbed.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenic and reproductive studies with animals have not been performed.
Pregnancy: Category C. Animal reproduction studies have not been conducted with GoLYTELY. It is also not known whether GoLYTELY can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. GoLYTELY should be given to a pregnant woman only if clearly needed.
Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Nausea, abdominal fullness and bloating are the most common adverse reactions (occurring in up to 50% of patients) to administration of GoLYTELY. Abdominal cramps, vomiting and anal irritation occur less frequently. These adverse reactions are transient and subside rapidly. Isolated cases of urticaria, rhinorrhea and dermatitis have been reported which may represent allergic reactions.

DOSAGE AND ADMINISTRATION
The recommended dose for adults is 4 liters of GoLYTELY solution prior to gastrointestinal examination, as ingestion of this dose produces a satisfactory preparation in over 95% of patients. Ideally the patient should fast for approximately three or four hours prior to GoLYTELY administration, but in no case should solid food be given for at least two hours before the solution is given.
GoLYTELY is usually administered orally, but may be given via nasogastric tube to patients who are unwilling or unable to drink the solution. **Oral administration** is at a rate of 240 ml (8 oz.) every 10 minutes, until 4 liters are consumed or the rectal effluent is clear. Rapid drinking of each portion is preferred to drinking small amounts continuously. **Nasogastric tube administration** is at the rate of 20–30 ml per minute (1.2–1.8 liters per hour). The first bowel movement should occur approximately one hour after the start of GoLYTELY administration.
Various regimens have been used. One method is to schedule patients for examination in midmorning or later, allowing the patients three hours for drinking and an additional one hour period for complete bowel evacuation. Another method is to administer GoLYTELY on the evening before the examination, particularly if the patient is to have a barium enema.
Preparation of the solution: GoLYTELY solution is prepared by filling the container to the 4 liter mark with water and shaking vigorously several times to insure that the ingredients are dissolved. Dissolution is facilitated by using lukewarm water. The solution is more palatable if chilled before administration. The reconstituted solution should be refrigerated and used within 48 hours. Discard any unused portion.

HOW SUPPLIED
In powdered form, for oral administration as a solution following reconstitution. Each disposable jug contains, in powdered form: polyethylene glycol 3350 236 g, sodium sulfate 22.74 g, sodium bicarbonate 6.74 g, sodium chloride 5.86 g, potassium chloride 2.97 g. When made up to 4 liters volume with water, the solution contains PEG 3350 17.6 mmol/L, sodium 125 mmol/L, sulfate 40 mmol/L, chloride 35 mmol/L, bicarbonate 20 mmol/L and potassium 10 mmol/L.

CAUTION
Federal law prohibits dispensing without prescription.

STORAGE
Store in sealed container at 59°–86°F. When reconstituted, keep solution refrigerated. Use within 48 hours. Discard unused portion.

Continued on next page

Merck Sharp & Dohme—Cont.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, during concomitant use of corticosteroids or ACTH, or after prolonged therapy.
Interference with adequate oral electrolyte intake will contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements such as foods with a high potassium content.
Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.
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 actual salt depletion, appropriate replacement is the therapy of choice.
Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazides.
Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes mellitus may become manifest during thiazide therapy.
Thiazides may increase the responsiveness to tubocurarine.
In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when HYDROPRES and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.
The antihypertensive effect of the drug may be enhanced in the postsympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.
If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.
Thiazides may decrease serum PBI levels without signs of thyroid disturbance.
Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.
Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Reserpine
Since reserpine may increase gastric secretion and motility, it should be used cautiously in patients with a history of peptic ulcer, ulcerative colitis, or other gastrointestinal disorder. This compound may precipitate biliary colic in patients with gallstones, or bronchial asthma in susceptible persons.
Reserpine may cause hypotension including orthostatic hypotension.
In hypertensive patients on reserpine therapy significant hypotension and bradycardia may develop during surgical anesthesia. The anesthesiologist should be aware that reserpine has been taken, since it may be necessary to give vagal blocking agents parenterally to prevent or reverse hypotension and/or bradycardia.
Anxiety or depression, as well as psychosis, may develop during reserpine therapy. If depression is present when therapy is begun, it may be aggravated. Mental depression is unusual with reserpine doses of 0.25 mg daily or less. In any case, HYDROPRES should be discontinued at the first sign of depression. Extreme caution should be used in treating patients with a history of mental depression, and the possibility of suicide should be kept in mind.
As with most antihypertensive therapy, caution should be exercised when treating hypertensive patients with renal insufficiency, since they adjust poorly to lowered blood pressure levels. Use reserpine cautiously with digitalis and quinidine; cardiac arrhythmias have occurred with reserpine preparations.
When two or more antihypertensives are given, the individual dosages may have to be reduced to prevent excessive drop in blood pressure. In hypertensive patients with coronary artery disease, it is important to avoid a precipitous drop in blood pressure.
Animal tumorigenicity: Rodent studies have shown that reserpine is an animal tumorigen, causing an increased incidence of mammary fibroadenomas in female mice, malignant tumors of the seminal vesicles in male mice, and malignant adrenal medullary tumors in male rats. These findings arose in 2 year studies in which the drug was administered in the feed at concentrations of 5 and 10 ppm—about 100 to 300 times the usual human dose. The breast neoplasms are thought to be related to reserpine's prolactin-elevating effect. Several other prolactin-elevating drugs have also been associated with an increased incidence of mammary neoplasia in rodents.
The extent to which these findings indicate a risk to humans is uncertain. Tissue culture experiments show that about one-third of human breast tumors are prolactin-dependent *in vitro*, a factor of considerable importance if the use of the drug is contemplated in a patient with previously detected breast cancer. The possibility of an increased risk of breast cancer in reserpine users has been studied extensively; however, no firm conclusion has emerged. Although a few epidemiologic studies have suggested a slightly increased risk (less than twofold in all studies except one) in women who have used reserpine, other studies of generally similar design have not confirmed this. Epidemiologic studies conducted using other drugs (neuroleptic agents) that, like reserpine, increase prolactin levels and therefore would be considered rodent mammary carcinogens, have not shown an association between chronic administration of the drug and human mammary tumorigenesis. While long-term clinical observation has not suggested such an association, the available evidence is considered too limited to be conclusive at this time. An association of reserpine intake with pheochromocytoma or tumors of the seminal vesicles has not been explored.

ADVERSE REACTIONS

Hydrochlorothiazide
Body as a Whole: Weakness.
Cardiovascular: Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).
Digestive: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis.
Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia.
Metabolic: Hyperglycemia, glycosuria, hyperuricemia, electrolyte imbalance (see PRECAUTIONS).
Musculoskeletal: Muscle spasm.
Nervous System/Psychiatric: Dizziness, vertigo, paresthesias, headache, restlessness.
Special Senses: Transient blurred vision, xanthopsia.
Hypersensitivity: Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.
Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.
Reserpine
Cardiovascular: Bradycardia, angina pectoris, arrhythmia, premature ventricular contractions, and other direct cardiac effects (e.g., fluid retention, congestive failure).
Digestive: Hypersecretion and increased motility, nausea, vomiting, anorexia, diarrhea, dryness of mouth, increased salivation.
Hematologic: Excessive bleeding following prostatic surgery, thrombocytopenic purpura.
Metabolic: Weight gain.
Musculoskeletal: Muscular aches.
Nervous System/Psychiatric: Excessive sedation, mental depression, nightmares, headache, dizziness, syncope, nervousness, paradoxical anxiety, central nervous system sensitization (dull sensorium, deafness, glaucoma, uveitis, optic atrophy), parkinsonism (usually reversible with decreased dosage or discontinuance of therapy).
Respiratory: Nasal congestion, dyspnea, epistaxis, enhanced susceptibility to colds.
Hypersensitivity: Flushing of skin, pruritus, rash.
Urogenital: Dysuria, nonpuerperal lactation, impotence, decreased libido.

DOSAGE AND ADMINISTRATION

The initial dosage of HYDROPRES should conform to the dosages of the individual components established during titration (see box warning).
The usual adult dosage of HYDROPRES 25 is 1 or 2 tablets once or twice a day; that of HYDROPRES 50 is 1 tablet once or twice a day. Dosage may require adjustment according to the blood pressure response of the patient.
Careful observations for changes in blood pressure must be made when HYDROPRES is used with other antihypertensive drugs.

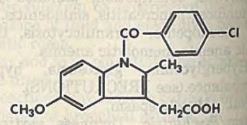
HOW SUPPLIED

No. 3265—Tablets HYDROPRES 25 are green, round, scored, compressed tablets, coded MSD 53. Each tablet contains 25 mg of hydrochlorothiazide and 0.125 mg of reserpine. They are supplied as follows:
NDC 0006-0053-68 in bottles of 100
NDC 0006-0053-82 in bottles of 1000.
Shown in Product Identification Section, page 418
No. 3266—Tablets HYDROPRES 50 are green, round, scored, compressed tablets, coded MSD 127. Each tablet contains 50 mg of hydrochlorothiazide and 0.125 mg of reserpine. They are supplied as follows:
NDC 0006-0127-68 in bottles of 100
NDC 0006-0127-82 in bottles of 1000.
Shown in Product Identification Section, page 418
A.H.F.S. Category: 24:08
DC 7414633 Issued October 1985

INDOCIN® Capsules, Oral Suspension and Suppositories (Indomethacin, MSD), U.S.P.
INDOCIN® SR Capsules (Indomethacin, MSD), U.S.P.

DESCRIPTION

INDOCIN® (Indomethacin, MSD) cannot be considered a simple analgesic and should not be used in conditions other than those recommended under INDICATIONS.
INDOCIN is supplied in four dosage forms. Capsules INDOCIN for oral administration contain either 25 mg or 50 mg of indomethacin and the following inactive ingredients: colloidal silicon dioxide, FD & C Blue 1, FD & C Red 3, gelatin, lactose, lecithin, magnesium stearate, and titanium dioxide. Capsules INDOCIN SR for sustained release oral administration contain 75 mg of indomethacin and the following inactive ingredients: cellulose, confectioner's sugar, FD & C Blue 1, FD & C Blue 2, FD & C Red 3, gelatin, hydroxypropyl methylcellulose, magnesium stearate, polyvinyl acetate-crotonic acid copolymer, starch, and titanium dioxide. Suspension INDOCIN for oral use contains 25 mg of indomethacin per 5 mL, alcohol 1%, and sorbic acid 0.1% added as a preservative and the following inactive ingredients: antifoam AF emulsion, flavors, purified water, sodium hydroxide or hydrochloric acid to adjust pH, sorbitol solution, tragacanth. Suppositories INDOCIN for rectal use contain 50 mg of indomethacin and the following inactive ingredients: glycerin, polyethylene glycol 8000, polyethylene glycol 3350, sodium chloride, edetic acid, butylated hydroxyanisole and butylated hydroxytoluene. Indomethacin is a non-steroidal anti-inflammatory indole derivative designated chemically as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid. Indomethacin is practically insoluble in water and sparingly soluble in alcohol. It has a pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali. The suspension has a pH of 4.0–5.0. The structural formula is:



CLINICAL PHARMACOLOGY

INDOCIN is a non-steroidal drug with anti-inflammatory, antipyretic and analgesic properties. Its mode of action, like that of other anti-inflammatory drugs, is not known. However, its therapeutic action is not due to pituitary-adrenal stimulation.
INDOCIN is a potent inhibitor of prostaglandin synthesis *in vitro*. Concentrations are reached during therapy which have been demonstrated to have an effect *in vivo* as well. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Moreover, prostaglandins are known to be among the mediators of inflammation. Since indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.
INDOCIN has been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.
INDOCIN affords relief of symptoms; it does not alter the progressive course of the underlying disease.
INDOCIN suppresses inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with INDOCIN for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased mobility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength.
Capsules INDOCIN have been found effective in relieving the pain, reducing the fever, swelling, redness, and tenderness of acute gouty arthritis. Capsules INDOCIN rather than Capsules INDOCIN SR are recommended for treatment of acute gouty arthritis—see INDICATIONS.
Following single oral doses of Capsules INDOCIN 25 mg or 50 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 mcg/mL, respec-

...at about 2 hours. Orally administered Capsules INDO... are virtually 100% bioavailable, with 90% of the dose ...bed within 4 hours. A single 50 mg dose of Oral Suspen... INDOCIN was found to be bioequivalent to a 50 mg IN... Capsule when each was administered with food.
...IN SR 75 mg are designed to release 25 mg ...ules INDOCIN SR 75 mg are designed to release 25 mg ...e drug initially and the remaining 50 mg over approxi... 12 hours (90% of dose absorbed by 12 hours). When ...ed over a 24-hour period, the cumulative amount and ...ourse of indomethacin absorption from a single Cap... INDOCIN SR are comparable to those of 3 doses of 25 mg ...ules INDOCIN given at 4–6 hour intervals.
...a concentrations of indomethacin fluctuate less and ...more sustained following administration of Capsules ...OCIN SR than following administration of 25 mg Cap... INDOCIN given at 4–6 hour intervals. In multiple-dose ...parisons, the mean daily steady-state plasma level of ...methacin attained with daily administration of Cap... INDOCIN SR 75 mg was indistinguishable from that ...ving Capsules INDOCIN 25 mg given at 0, 6 and 12 ...s daily. However, there was a significant difference in ...methacin plasma levels between the two dosage regi... especially after 12 hours.
...lled clinical studies of safety and efficacy in patients ...osteoarthritis have shown that one Capsule INDOCIN ...as clinically comparable to one 25 mg Capsule INDO... t.i.d.; and in controlled clinical studies in patients with ...matoid arthritis, one Capsule INDOCIN SR taken in the ...ing and one in the evening were clinically indistin... from one 50 mg Capsule INDOCIN t.i.d.
...methacin is eliminated via renal excretion, metabolism, ...liary excretion. Indomethacin undergoes appreciable ...-hepatic circulation. The mean half-life of indomethacin ...estimated to be about 4.5 hours. With a typical therapeutic regimen of 25 or 50 mg t.i.d., the steady-state plasma concentrations of indomethacin are an average 1.4 times ...following the first dose.
...rate of absorption is more rapid from the rectal suppository than from Capsules INDOCIN. Ordinarily, therefore, ...total amount absorbed from the suppository would be ...ected to be at least equivalent to the capsule. In controlled clinical trials, however, the amount of indomethacin ...rbed was found to be somewhat less (80–90%) than that ...rbed from Capsules INDOCIN. This is probably because ...e subjects did not retain the material from the suppository for the one hour necessary to assure complete absorption. Since the suppository dissolves rather quickly rather ...melting slowly, it is seldom recovered in recognizable ...if the patient retains the suppository for more than a ...minutes.
...methacin exists in the plasma as the parent drug and its ...methyl, desbenzoyl, and desmethyl-desbenzoyl metabo..., all in the unconjugated form. About 60 percent of an ...dosage is recovered in urine as drug and metabolites (26 ...ent as indomethacin and its glucuronide), and 33 percent ...covered in feces (1.5 percent as indomethacin).
...t 99% of indomethacin is bound to protein in plasma ...r the expected range of therapeutic plasma concentra...
...gastroscopic study in 45 healthy subjects, the number of ...ric mucosal abnormalities was significantly higher in ...group receiving Capsules INDOCIN than in the group ...ng Suppositories INDOCIN or placebo.
...double-blind comparative clinical study involving 175 ...ents with rheumatoid arthritis, however, the incidence ...per gastrointestinal adverse effects with Suppositories ...apsules INDOCIN was comparable. The incidence of ...er gastrointestinal adverse effects was greater in the ...ository group.

...DICATIONS
...methacin has been found effective in active stages of the ...owing:
...derate to severe rheumatoid arthritis including acute ...ses of chronic disease.
...derate to severe ankylosing spondylitis.
...derate to severe osteoarthritis.
...ute painful shoulder (bursitis and/or tendinitis).
...ute gouty arthritis.
...ules INDOCIN SR are recommended for all of the indi...ns for Capsules INDOCIN except acute gouty arthritis.
...OCIN may enable the reduction of steroid dosage in pa... receiving steroids for the more severe forms of rheu...oid arthritis. In such instances the steroid dosage should ...duced slowly and the patients followed very closely for ...possible adverse effects.
...use of INDOCIN in conjunction with aspirin or other ...ylates is not recommended. Controlled clinical studies ...e shown that the combined use of INDOCIN and aspirin ...not produce any greater therapeutic effect than the use ...NDOCIN alone. Furthermore, in one of these clinical ...es, the incidence of gastrointestinal side effects was ...ificantly increased with combined therapy (see DRUG ...ERACTIONS).

CONTRAINDICATIONS

INDOCIN should not be used in:
Patients who are hypersensitive to this product.
Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.
Suppositories INDOCIN are contraindicated in patients with a history of proctitis or recent rectal bleeding.

WARNINGS

General:
Because of the variability of the potential of INDOCIN to cause adverse reactions in the individual patient, the following are strongly recommended:
1. The lowest possible effective dose for the individual patient should be prescribed. Increased dosage tends to increase adverse effects, particularly in doses over 150–200 mg/day, without corresponding increase in clinical benefits.
2. Careful instructions to, and observations of, the individual patient are essential to the prevention of serious adverse reactions. As advancing years appear to increase the possibility of adverse reactions, INDOCIN should be used with greater care in the aged.
3. Effectiveness of INDOCIN in children has not been established. INDOCIN should not be prescribed for children 14 years of age and younger unless toxicity or lack of efficacy associated with other drugs warrants the risk.
   In experience with more than 900 children reported in the literature or to Merck Sharp and Dohme who were treated with Capsules INDOCIN, side effects in children were comparable to those reported in adults. Experience in children has been confined to the use of Capsules INDOCIN.
   If a decision is made to use indomethacin for children two years of age or older, such patients should be monitored closely and periodic assessment of liver function is recommended. There have been cases of hepatotoxicity reported in children with juvenile rheumatoid arthritis, including fatalities.
   If indomethacin treatment is instituted, a suggested starting dose is 2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 4 mg/kg/day or 150–200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level required to control symptoms, or the drug should be discontinued.
4. If Capsules INDOCIN SR are used for initial therapy or during dosage adjustment, observe the patient closely (see DOSAGE AND ADMINISTRATION).

Gastrointestinal Effects:
Single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestine, have been reported to occur with INDOCIN. Fatalities have been reported in some instances. Rarely, intestinal ulceration has been associated with stenosis and obstruction.
Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) have occurred. Increased abdominal pain in ulcerative colitis patients or the development of ulcerative colitis and regional ileitis have been reported to occur rarely.
Because of the occurrence, and at times severity, of gastrointestinal reactions to INDOCIN, the prescribing physician must be continuously alert for any sign or symptom signaling a possible gastrointestinal reaction. The risks of continuing therapy with INDOCIN in the face of such symptoms must be weighed against the possible benefits to the individual patient.
INDOCIN should not be given to patients with active gastrointestinal lesions or with a history of recurrent gastrointestinal lesions except under circumstances which warrant the very high risk and where patients can be monitored very closely.
The gastrointestinal effects may be reduced by giving Capsules INDOCIN or Capsules INDOCIN SR immediately after meals, with food, or with antacids.
Renal Effects:
As with other non-steroidal anti-inflammatory drugs, long term administration of indomethacin 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 and renal 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 conditions such as renal or hepatic dysfunction, complications associated with advanced age, extracellular volume depletion from any cause, congestive heart failure, sepsis, or concomitant use of any nephrotoxic drug. INDOCIN or other NSAIDs should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.
Increases in serum potassium concentration, including hyperkalemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state (see PRECAUTIONS, *Drug Interactions*).
Since INDOCIN is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be anticipated to avoid excessive drug accumulation.
Ocular Effects:
Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with INDOCIN. The prescribing physician should be alert to the possible association between the changes noted and INDOCIN. It is advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients where therapy is prolonged.
Central Nervous System Effects:
INDOCIN may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. If severe CNS adverse reactions develop, INDOCIN should be discontinued.
INDOCIN may cause drowsiness; therefore, patients should be cautioned about engaging in activities requiring mental alertness and motor coordination, such as driving a car. INDOCIN may also cause headache. Headache which persists despite dosage reduction requires cessation of therapy with INDOCIN.
Use in Pregnancy and the Neonatal Period
INDOCIN is not recommended for use in pregnant women, since safety for use has not been established, and because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of the ductus arteriosus) during the third trimester of pregnancy.
Teratogenic studies were conducted in mice and rats at dosages of 0.5, 1.0, 2.0, and 4.0 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day considered secondary to the decreased average fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5 to 15 mg/kg/day) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. Comparable studies in rodents using high doses of aspirin have shown similar maternal and fetal effects.
As with other non-steroidal anti-inflammatory agents which inhibit prostaglandin synthesis, indomethacin has been found to delay parturition in rats.
In rats and mice, 4.0 mg/kg/day given during the last three days of gestation caused a decrease in maternal weight gain and some maternal and fetal deaths. An increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses was observed. At 2.0 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups. Administration of 0.5 or 4.0 mg/kg/day during the first three days of life did not cause an increase in neuronal necrosis at either dose level.
Use in Nursing Mothers
INDOCIN is excreted in the milk of lactating mothers. INDOCIN is not recommended for use in nursing mothers.

PRECAUTIONS

INDOCIN may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing controlled infection.
Fluid retention and peripheral edema have been observed in some patients taking INDOCIN. Therefore, as with other non-steroidal anti-inflammatory drugs, INDOCIN should be used with caution in patients with cardiac dysfunction, hypertension, or other conditions predisposing to fluid retention.
In a study of patients with severe heart failure and hyponatremia, INDOCIN was associated with significant deterioration of circulatory hemodynamics, presumably due to inhibition of prostaglandin dependent compensatory mechanisms.

Continued on next page

Merck Sharp & Dohme—Cont.

INDOCIN, like other non-steroidal anti-inflammatory agents, can inhibit platelet aggregation. This effect is of shorter duration than that seen with aspirin and usually disappears within 24 hours after discontinuation of INDOCIN. INDOCIN has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this effect may be exaggerated in patients with underlying hemostatic defects, INDOCIN should be used with caution in persons with coagulation defects.

As with other non-steroidal 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 INDOCIN. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with INDOCIN as with other non-steroidal anti-inflammatory drugs. 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.), INDOCIN should be discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In an 81-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day, indomethacin had no tumorigenic effect. Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat (dosing period 73–110 weeks) and the mouse (dosing period 62–88 weeks) at doses up to 1.5 mg/kg/day.

Indomethacin did not have any mutagenic effect in *in vitro* bacterial tests (Ames test and *E. coli* with or without metabolic activation) and a series of *in vivo* tests including the host-mediated assay, sex-linked recessive lethals in *Drosophila,* and the micronucleus test in mice.

Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study or a two litter reproduction study in rats.

Drug Interactions

In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin. In some patients, combined use of INDOCIN and diflunisal has been associated with fatal gastrointestinal hemorrhage. Therefore, diflunisal and INDOCIN should not be used concomitantly.

In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of aspirin per day decreases indomethacin blood levels approximately 20%.

Clinical studies have shown that INDOCIN does not influence the hypoprothrombinemia produced by anticoagulants. However, when any additional drug, including INDOCIN, is added to the treatment of patients on anticoagulant therapy, the patients should be observed for alterations of the prothrombin time.

When INDOCIN is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased. Therefore, a lower total daily dosage of INDOCIN may produce a satisfactory therapeutic effect. When increases in the dose of INDOCIN are made, they should be made carefully and in small increments.

Capsules INDOCIN 50 mg t.i.d. produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis. As a consequence, when INDOCIN and lithium are given concomitantly, the patient should be carefully observed for signs of lithium toxicity. (Read circulars for lithium preparations before use of such concomitant therapy.) In addition, the frequency of monitoring serum lithium concentration should be increased at the outset of such combination drug treatment.

In some patients, the administration of INDOCIN can reduce the diuretic, natriuretic, and, antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when INDOCIN and diuretics are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

INDOCIN reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

It has been reported that the addition of triamterene to a maintenance schedule of INDOCIN resulted in reversible acute renal failure in two of four healthy volunteers. INDOCIN and triamterene should not be administered together.

INDOCIN and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of INDOCIN and potassium-sparing diuretics on potassium kinetics and renal function should be considered when these agents are administered concurrently.

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by INDOCIN.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by non-steroidal anti-inflammatory drugs including INDOCIN has been reported. Therefore, when using these blocking agents to treat hypertension, patients should be observed carefully in order to confirm that the desired therapeutic effect has been obtained. There are reports that INDOCIN can reduce the antihypertensive effect of captopril in some patients.

Pediatric Use

Effectiveness in children 14 years of age and younger has not been established (see WARNINGS).

ADVERSE REACTIONS

The adverse reactions for Capsules INDOCIN listed in the following table have been arranged into two groups: (1) incidence greater than 1%; and (2) incidence less than 1%. The incidence for group (1) was obtained from 33 double-blind controlled clinical trials reported in the literature (1,081 patients). The incidence for group (2) was based on reports in clinical trials, in the literature, and on voluntary reports since marketing. The probability of a causal relationship exists between INDOCIN and these adverse reactions, some of which have been reported only rarely.

In controlled clinical trials, the incidence of adverse reactions to Capsules INDOCIN SR and equal 24-hour doses of Capsules INDOCIN were similar.

The adverse reactions reported with Capsules INDOCIN may occur with use of the suppositories. In addition, rectal irritation and tenesmus have been reported in patients who have received the suppositories.

The adverse reactions reported with Capsules INDOCIN may also occur with use of the suspension.

[See table left].

Incidence greater than 1%	*Incidence less than 1%*	
GASTROINTESTINAL		
nausea* with or without vomiting	anorexia	gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.)
dyspepsia* (including indigestion, heartburn and epigastric pain)	bloating (includes distention)	development of ulcerative colitis and regional ileitis
diarrhea	flatulence	ulcerative stomatitis
abdominal distress or pain	peptic ulcer gastroenteritis	toxic hepatitis and jaundice (some fatal cases have been reported)
constipation	rectal bleeding	
	proctitis	
	single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestines	
	intestinal ulceration associated with stenosis and obstruction	
CENTRAL NERVOUS SYSTEM		
headache (11.7%)	anxiety (includes nervousness)	light-headedness
dizziness*	muscle weakness	syncope
vertigo	involuntary muscle movements	paresthesia
somnolence	insomnia	aggravation of epilepsy and parkinsonism
depression and fatigue (including malaise and listlessness)	muzziness	depersonalization
	psychic disturbances including psychotic episodes	coma
	mental confusion	peripheral neuropathy
	drowsiness	convulsions
SPECIAL SENSES		
tinnitus	ocular—corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients on prolonged therapy with INDOCIN	blurred vision
		diplopia
		hearing disturbances, deafness

Causal relationship unknown: Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to physicians:

Hematologic: Although there have been several reports of leukemia, the supporting information is weak.

Genitourinary: Urinary frequency.

OVERDOSAGE

The following symptoms may be observed following overdosage: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, or lethargy. There have been reports of paresthesias, numbness, and convulsions.

Treatment is symptomatic and supportive. The stomach should be emptied as quickly as possible if the ingestion is recent. If vomiting has not occurred spontaneously, the patient should be induced to vomit with syrup of ipecac. If the patient is unable to vomit, gastric lavage should be performed. Once the stomach has been emptied, 25 or 50 g of activated charcoal may be given. Depending on the condition of the patient, close medical observation and nursing care may be required. The patient should be followed for several days because gastrointestinal ulceration and hemorrhage have been reported as adverse reactions of indomethacin. Use of antacids may be helpful.

The oral LD_{50} of indomethacin in mice and rats (based on 14 day mortality response) was 50 and 12 mg/kg, respectively.

DOSAGE AND ADMINISTRATION

INDOCIN is available as 25 and 50 mg Capsules INDOCIN, 75 mg Capsules INDOCIN SR for oral use, Oral Suspension INDOCIN, containing 25 mg of indomethacin per 5 mL, and 50 mg Suppositories INDOCIN for rectal use. Capsules INDOCIN SR 75 mg once a day can be substituted for Capsules INDOCIN 25 mg t.i.d. However, there will be significant differences between the two dosage regimens in indomethacin blood levels, especially after 12 hours (see CLINICAL PHARMACOLOGY). In addition, Capsules INDOCIN SR 75 mg b.i.d. can be substituted for Capsules INDOCIN 50 mg t.i.d.

[Continued following page]

VASCULAR	hypertension	congestive heart failure
	hypotension	arrhythmia; palpitations
	tachycardia	
	chest pain	
BOLIC	edema	hyperglycemia
	weight gain	glycosuria
	fluid retention	hyperkalemia
	flushing or sweating	
UMENTARY	pruritus	exfoliative dermatitis
	rash; urticaria	erythema nodosum
	petechiae or ecchymosis	loss of hair
		Stevens-Johnson syndrome
		erythema multiforme
		toxic epidermal necrolysis
TOLOGIC	leukopenia	aplastic anemia
	bone marrow depression	hemolytic anemia
	anemia secondary to obvious or occult gastrointestinal bleeding	agranulocytosis
		thrombocytopenic purpura
SENSITIVITY	acute anaphylaxis	dyspnea
	acute respiratory distress	asthma
		purpura
	rapid fall in blood pressure resembling a shock-like state	angiitis
		pulmonary edema
	angioedema	
OURINARY	hematuria	BUN elevation
	vaginal bleeding	renal insufficiency, including renal failure
	proteinuria	
	nephrotic syndrome	
	interstitial nephritis	
LLANEOUS	epistaxis	
	breast changes, including enlargement and tenderness, or gynecomastia	

tions occurring in 3% to 9% of patients treated with INDOCIN. (Those reactions occurring in less than 3% of the pa- are unmarked.)

s INDOCIN SR may be substituted for all the indica- Capsules INDOCIN except acute gouty arthritis. reactions appear to correlate with the size of the INDOCIN in most patients but not all. Therefore, fort should be made to determine the smallest effec- age for the individual patient.

give Capsules INDOCIN, Capsules INDOCIN SR, or spension INDOCIN with food, immediately after or with antacids to reduce gastric irritation.

Use

IN ordinarily should not be prescribed for children 14 age and under (see WARNINGS).

Recommendations for Active Stages of the Follow-

rate to severe rheumatoid arthritis including acute of chronic disease; moderate to severe ankylosing ylitis; and moderate to severe osteoarthritis.

sted Dosage:

les INDOCIN 25 mg b.i.d. or t.i.d. If this is well toler- increase the daily dosage by 25 or by 50 mg, if re- d by continuing symptoms, at weekly intervals until sfactory response is obtained or until a total daily of 150–200 mg is reached. DOSES ABOVE THIS UNT GENERALLY DO NOT INCREASE THE EF- IVENESS OF THE DRUG.

nts who have persistent night pain and/or morning , the giving of a large portion, up to a maximum of of the total daily dose at bedtime, either orally or by uppositories, may be helpful in affording relief. The ily dose should not exceed 200 mg. In acute flares of rheumatoid arthritis, it may be necessary to increase ge by 25 mg or, if required, by 50 mg daily.

les INDOCIN SR 75 mg are used for initiating indo- n treatment, one capsule daily should be the usual dose in order to observe patient tolerance since 75 ay is the maximum recommended starting dose for hacin (see above). If Capsules INDOCIN SR are used ase the daily dose, patients should be observed for signs and symptoms of intolerance since the daily increment will exceed the daily increment recommended for the other dosage forms. For patients who require 150 mg of INDOCIN per day and have demonstrated acceptable tolerance, INDOCIN SR may be prescribed as one capsule twice daily.

If minor adverse effects develop as the dosage is increased, reduce the dosage rapidly to a tolerated dose and OBSERVE THE PATIENT CLOSELY.

If severe adverse reactions occur, STOP THE DRUG. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is receiving the smallest effective dose or the drug is discontinued.

Careful instructions to, and observations of, the individual patient are essential to the prevention of serious, irreversible, including fatal, adverse reactions.

As advancing years appear to increase the possibility of adverse reactions, INDOCIN should be used with greater care in the aged.

2. Acute painful shoulder (bursitis and/or tendinitis).
   Initial Dose:
   75–150 mg daily in 3 or 4 divided doses.
   The drug should be discontinued after the signs and symptoms of inflammation have been controlled for several days. The usual course of therapy is 7–14 days.
3. Acute gouty arthritis.
   Suggested Dosage:
   Capsules INDOCIN 50 mg t.i.d. until pain is tolerable. The dose should then be rapidly reduced to complete cessation of the drug. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

HOW SUPPLIED

No. 3316—Capsules INDOCIN, 25 mg are opaque blue and white capsules, coded MSD 25. They are supplied as follows:
NDC 0006-0025-68 bottles of 100
(6505-00-926-2154, 25 mg 100's)
NDC 0006-0025-78 unit of use bottles of 100
NDC 0006-0025-28 unit dose packages of 100
(6505-00-118-2776, 25 mg individually sealed 100's)
NDC 0006-0025-82 bottles of 1000
(6505-00-931-0680, 25 mg 1000's).
Shown in Product Identification Section, page 418

No. 3317—Capsules INDOCIN, 50 mg are opaque blue and white capsules, coded MSD 50. They are supplied as follows:
NDC 0006-0050-68 bottles of 100
NDC 0006-0050-28 unit dose packages of 100.
Shown in Product Identification Section, page 418

No. 3376—Oral Suspension INDOCIN, 25 mg per 5 mL, is an off-white suspension with a pineapple coconut mint flavor. It is supplied as follows:
NDC 0006-3376-66 in bottles of 237 mL.

Storage
Store below 30°C (86°F). Avoid temperatures above 50°C (122°F). Protect from freezing.

No. 3370—Capsules INDOCIN SR, 75 mg each, are capsules with an opaque blue cap and clear body containing a mixture of blue and white pellets, coded MSD 693. They are supplied as follows:
NDC 0006-0693-31 unit of use bottles of 30
(6505-01-135-7391, 75 mg 30's)
NDC 0006-0693-61 unit of use bottles of 60
(6505-01-137-4629, 75 mg 60's).
Shown in Product Identification Section, page 418

No. 3354—Suppositories INDOCIN, 50 mg each, are white, opaque, rectal suppositories and are supplied as follows:
NDC 0006-0150-30, boxes of 30.
Shown in Product Identification Section, page 418

Suppositories INDOCIN are distributed by:
MERCK SHARP & DOHME, Division of Merck & Co., INC.
West Point, Pa. 19486
Manufactured by:
MERCK SHARP & DOHME
(Italia) S.p.A.
27100—Pavia, Italy
Capsules and Oral Suspension INDOCIN® and INDOCIN® SR are distributed and manufactured by:
MERCK SHARP & DOHME, Division of Merck & Co., INC.
West Point, Pa. 19486

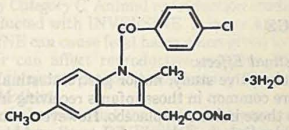
A.H.F.S. Category: 28:08
DC 7342912 Issued January 1987

INDOCIN® I.V. ℞
(Indomethacin Sodium Trihydrate, MSD)

DESCRIPTION

Sterile INDOCIN® I.V. (Indomethacin Sodium Trihydrate, MSD) for intravenous administration is lyophilized indomethacin sodium trihydrate. Each vial contains indomethacin sodium trihydrate equivalent to 1 mg indomethacin as a white to yellow lyophilized powder or plug. Variations in the size of the lyophilized plug and the intensity of color have no relationship to the quality or amount of indomethacin present in the vial.

Indomethacin sodium trihydrate is designated chemically as 1-(4-chlorobenzoyl) -5- methoxy-2-methyl-1*H* -indole-3-acetic acid, sodium salt, trihydrate. Its molecular weight is 433.8. Its empirical formula is $C_{19}H_{15}ClNNaO_4 \cdot 3H_2O$ and its structural formula is:



CLINICAL PHARMACOLOGY

Although the exact mechanism of action through which indomethacin causes closure of a patent ductus arteriosus is not known, it is believed to be through inhibition of prostaglandin synthesis. Indomethacin has been shown to be a potent inhibitor of prostaglandin synthesis, both *in vitro* and *in vivo*. In human newborns with certain congenital heart malformations, PGE 1 dilates the ductus arteriosus. In fetal and newborn lambs, E type prostaglandins have also been shown to maintain the patency of the ductus, and as in human newborns, indomethacin causes its constriction.

Continued on next page

Upjohn—Cont.

creted in human milk. Because the potential for hypoglycemia in nursing infants may exist, 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. If the drug is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypoglycemia: See Precautions and Overdosage Sections.

Gastrointestinal Reactions: Cholestatic jaundice may occur rarely; MICRONASE Tablets (glyburide) should be discontinued if this occurs.

Liver function abnormalities, including isolated transaminase elevations, have been reported.

Gastrointestinal disturbances, *e.g.*, nausea, epigastric fullness, and heartburn are the most common reactions, having occurred in 1.8% of treated patients during clinical trials. They tend to be dose related and may disappear when dosage is reduced.

Dermatologic Reactions: Allergic skin reactions, *e.g.*, pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions occurred in 1.5% of treated patients during clinical trials. These may be transient and may disappear despite continued use of MICRONASE; if skin reactions persist, the drug should be discontinued.

Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic Reactions: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas; however, hepatic porphyria has not been reported with MICRONASE and disulfiram-like reactions have been reported very rarely.

Cases of hyponatremia have been reported with glyburide and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

OVERDOSAGE

Overdosage of sulfonylureas, including MICRONASE Tablets (glyburide), can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate which will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with MICRONASE Tablets (glyburide) or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, *i.e.*, inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, *i.e.*, loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short-term administration of MICRONASE may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

Usual Starting Dose

The usual starting dose of MICRONASE Tablets is 2.5 to 5.0 mg daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1.25 mg daily. (See Precautions Sections for patients at increased risk.) Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Transfer From Other Hypoglycemic Therapy

Patients Receiving Other Oral Antidiabetic Therapy: Transfer of patients from other oral antidiabetic regimens to MICRONASE should be done conservatively and the initial daily dose should be 2.5 to 5 mg. When transferring patients from oral hypoglycemic agents other than chlorpropamide to MICRONASE, no transition period and no initial or priming dose are necessary. When transferring patients from chlorpropamide, particular care should be exercised during the first two weeks because the prolonged retention of chlorpropamide in the body and subsequent overlapping drug effects may provoke hypoglycemia.

Patients Receiving Insulin: Some type II diabetic patients being treated with insulin may respond satisfactorily to MICRONASE. If the insulin dose is less than 20 units daily, substitution of MICRONASE Tablets 2.5 to 5.0 mg as a single daily dose may be tried. If the insulin dose is between 20 and 40 units daily, the patient may be placed directly on MICRONASE Tablets 5.0 mg daily as a single dose. If the insulin dose is more than 40 units daily, a transition period is required for conversion to MICRONASE. In these patients, insulin dosage is decreased by 50% and MICRONASE Tablets 5 mg daily is started. Please refer to Titration to Maintenance Dose for further explanation.

Titration to Maintenance Dose

The usual maintenance dose is in the range of 1.25 to 20 mg daily, which may be given as a single dose or in divided doses (See Dosage Interval Section). Dosage increases should be made in increments of no more than 2.5 mg at weekly intervals based upon the patient's blood glucose response.

No exact dosage relationship exists between MICRONASE and the other oral hypoglycemic agents. Although patients may be transferred from the maximum dose of other sulfonylureas, the maximum starting dose of 5.0 mg of MICRONASE Tablets should be observed. A maintenance dose of 5 mg of MICRONASE Tablets provides approximately the same degree of blood glucose control as 250 to 375 mg chlorpropamide, 250 to 375 mg tolazamide, 500 to 750 mg acetohexamide, or 1000 to 1500 mg tolbutamide.

When transferring patients receiving more than 40 units of insulin daily, they may be started on a daily dose of MICRONASE Tablets 5 mg concomitantly with a 50% reduction in insulin dose. Progressive withdrawal of insulin and increase of MICRONASE in increments of 1.25 to 2.5 mg every 2 to 10 days is then carried out. During this conversion period when both insulin and MICRONASE are being used, hypoglycemia may rarely occur. During insulin withdrawal, patients should test their urine for glucose and acetone at least three times daily and report results to their physician. The appearance of persistent acetonuria with glycosuria indicates that the patient is a type I diabetic who requires insulin therapy.

Maximum Dose

Daily doses of more than 20 mg are not recommended.

Dosage Interval

Once-a-day therapy is usually satisfactory. Some patients, particularly those receiving more than 10 mg daily, may have a more satisfactory response with twice-a-day dosage.

Specific Patient Populations

MICRONASE is not recommended for use in pregnancy or for use in children.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions. (See Precautions Section.)

HOW SUPPLIED

MICRONASE Tablets (glyburide), scored, round, are available in the following strengths, colors and sizes:

1.25 mg	White	Bottles of 100	NDC 0009-0131-01
2.5 mg	Dark Pink	Bottles of 30	NDC 0009-0141-06
2.5 mg	Dark Pink	Bottles of 60	NDC 0009-0141-07
2.5 mg	Dark Pink	Bottles of 100	NDC 0009-0141-01
2.5 mg	Dark Pink	Unit Dose Pkg,. of 100	NDC 0009-0141-02
5 mg	Blue	Bottles of 30	NDC 0009-0171-08
5 mg	Blue	Bottles of 60	NDC 0009-0171-09
5 mg	Blue	Bottles of 90	NDC 0009-0171-10
5.0 mg	Blue	Bottles of 100	NDC 0009-0171-01
5.0 mg	Blue	Bottles of 500	NDC 0009-0171-02
5.0 mg	Blue	Unit Dose Pkg. of 100	NDC 0009-0171-03
5 mg	Blue	Bottles of 1000	NDC 0009-0171-04

Caution: Federal law prohibits dispensing without prescription. Store at controlled room temperature 15°–30° C (59°–86° F). Dispensed in well closed containers with safety closures. Keep container tightly closed.

Code 811 985 211

Shown in Product Identification Section, page 433

MOTRIN®

℞

brand of ibuprofen tablets, USP

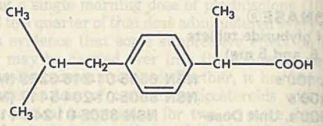
800 mg, 100's NSN 6505-01-214-9061 (VA)

800 mg, 500's NSN 6505-01-214-9062 (M & VA)

DESCRIPTION

MOTRIN Tablets contain the active ingredient ibuprofen, which is (±)-2-(*p*-isobutylphenyl) propionic acid. Ibuprofen is a white powder with a melting point of 74–77°C and is very slightly soluble in water (< 1 mg/ml) and readily soluble in organic solvents such as ethanol and acetone.

The structural formula is represented below:



MOTRIN, a nonsteroidal anti-inflammatory agent, is available in 300 mg, 400 mg, 600 mg, and 800 mg tablets for oral administration.

Inactive ingredients: **300 mg**—acacia, acetylated monoglyceride, calcium sulfate, carboxymethylcellulose sodium, carnauba wax, colloidal silicon dioxide, corn starch, povidone, pregelatinized starch, sesame oil, shellac, stearic acid, sucrose, white wax; **400 mg**—acacia, acetylated monoglyceride, calcium sulfate, carboxymethylcellulose sodium, carnauba wax, colloidal silicon dioxide, corn starch, FD&C yellow no. 6, pregelatinized starch, povidone, sesame oil, shellac, sodium benzoate, stearic acid, sucrose, titanium dioxide, white wax; **600 mg**—carnauba wax, colloidal silicon dioxide, corn starch, FD&C yellow no. 6, hydroxypropyl cellulose, hydroxypropyl methylcellulose, pregelatinized starch, propylene glycol, stearic acid, titanium dioxide; **800 mg**—carnauba wax, colloidal silicon dioxide, croscarmellose sodium, FD&C yellow no. 6, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, propylene glycol, talc, titanium dioxide.

CLINICAL PHARMACOLOGY

MOTRIN Tablets contain ibuprofen which possesses analgesic and antipyretic activities. Its mode of action, like that of other nonsteroidal anti-inflammatory agents, is not completely understood, but may be related to prostaglandin synthetase inhibition.

In clinical studies in patients with rheumatoid arthritis and osteoarthritis, MOTRIN has been shown to be comparable to aspirin in controlling pain and inflammation and to be associated with a statistically significant reduction in the milder gastrointestinal side effects (see ADVERSE REACTIONS). MOTRIN may be well tolerated in some patients who have had gastrointestinal side effects with aspirin, but these patients when treated with MOTRIN should be carefully followed for signs and symptoms of gastrointestinal ulceration and bleeding. Although it is not definitely known whether MOTRIN causes less peptic ulceration than aspirin, in one study involving 885 patients with rheumatoid arthritis treated for up to one year, there were no reports of gastric ulceration with MOTRIN whereas frank ulceration was reported in 13 patients in the aspirin group (statistically significant $p < .001$).

Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is approximately half that seen with aspirin. Studies using ^{51}Cr-tagged red cells indicate that fecal blood loss associated with MOTRIN Tablets in doses up to 2400 mg daily did not exceed the normal range, and was significantly less than that seen in aspirin-treated patients.

In clinical studies in patients with rheumatoid arthritis, MOTRIN has been shown to be comparable to indomethacin in controlling the signs and symptoms of disease activity and to be associated with a statistically significant reduction of the milder gastrointestinal (see ADVERSE REACTIONS) and CNS side effects.

MOTRIN may be used in combination with gold salts and/or corticosteroids.

Controlled studies have demonstrated that MOTRIN is a more effective analgesic than propoxyphene for the relief of episiotomy pain, pain following dental extraction procedures, and for the relief of the symptoms of primary dysmenorrhea.

In patients with primary dysmenorrhea, MOTRIN has been shown to reduce elevated levels of prostaglandin activity in the menstrual fluid and to reduce resting and active intrauterine pressure, as well as the frequency of uterine contractions. The probable mechanism of action is to inhibit prostaglandin synthesis rather than simply to provide analgesia.

The ibuprofen in MOTRIN is rapidly absorbed when administered orally. Peak serum ibuprofen levels are generally attained one to two hours after administration. With single doses up to 800 mg, a linear relationship exists between amount of drug administered and the integrated area under

the serum drug concentration vs time curve. Above 800 mg, however, the area under the curve increases less than proportional to increases in dose. There is no evidence of drug accumulation or enzyme induction.

The administration of MOTRIN Tablets either under fasting conditions or immediately before meals yields quite similar serum ibuprofen concentration-time profiles. When MOTRIN is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption. The bioavailability of the drug is minimally altered by the presence of food.

A bioavailability study has shown that there was no interference with the absorption of ibuprofen when MOTRIN was given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide.

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. The serum half-life is 1.8 to 2.0 hours.

Studies have shown that following ingestion of the drug, 45% to 79% of the dose was recovered in the urine within 24 hours as metabolite A (25%), (+)-2-[*p*-(2hydroxymethylpropyl)- phenyl] propionic acid and metabolite B (37%), (+)-2-[*p*-(2carboxypropyl)-phenyl] propionic acid; the percentages of free and conjugated ibuprofen were approximately 1% and 14%, respectively.

INDICATIONS AND USAGE

MOTRIN Tablets (ibuprofen) are indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

MOTRIN is indicated for relief of mild to moderate pain.

MOTRIN is also indicated for the treatment of primary dysmenorrhea.

Since there have been no controlled clinical trials to demonstrate whether or not there is any beneficial effect or harmful interaction with the use of MOTRIN in conjunction with aspirin, the combination cannot be recommended (see **Drug Interactions**).

Controlled clinical trials to establish the safety and effectiveness of MOTRIN in children have not been conducted.

CONTRAINDICATIONS

MOTRIN Tablets (ibuprofen) should not be used in patients who have previously exhibited hypersensitivity to the drug, or in individuals with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported in patients receiving MOTRIN Tablets (ibuprofen). Peptic ulceration, perforation, or severe gastrointestinal bleeding can have a fatal outcome, and although a few such reports have been received with MOTRIN, cause and effect relationship has not been established. MOTRIN should be given under close supervision to patients with a history of upper gastrointestinal tract disease, and early after consulting the ADVERSE REACTIONS section.

In patients with active peptic ulcer and active rheumatoid arthritis, attempts should be made to treat the arthritis with nonulcerogenic drugs, such as gold. If MOTRIN must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

PRECAUTIONS

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving MOTRIN Tablets (ibuprofen), the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with MOTRIN; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

MOTRIN, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation but the effect is quantitatively less and of shorter duration than that seen with aspirin. MOTRIN has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, MOTRIN should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on MOTRIN should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when MOTRIN is added to the treatment program.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious noninflammatory painful conditions.

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 MOTRIN. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. 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 (eg, eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with doses ranging from 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. This has been observed with other nonsteroidal anti-inflammatory drugs; the mechanism is unknown. With daily doses of 3200 mg, the total decrease in hemoglobin may exceed 1 gram; if there are no signs of bleeding, it is probably not clinically important. In two postmarketing clinical studies the incidence of a decreased hemoglobin level was greater than previously reported. Decrease in hemoglobin of 1 gram or more was observed in 17.1% of 193 patients on 1600 mg ibuprofen daily (osteoarthritis), and in 22.8% of 189 patients taking 2400 mg of ibuprofen daily (rheumatoid arthritis). Positive stool occult blood tests and elevated serum creatinine levels were also observed in these studies.

Aseptic Meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on MOTRIN, the possibility of its being related to MOTRIN should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long term administration of ibuprofen 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 a nonsteroidal anti-inflammatory drug 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 nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Those patients at high risk who chronically take MOTRIN should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Drug Interactions: *Coumarin-type anticoagulants.* Several short-term controlled studies failed to show that MOTRIN significantly affected prothrombin times or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. However, because bleeding has been reported when MOTRIN and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants, the physician should be cautious when administering MOTRIN to patients on anticoagulants.

Aspirin: Animal studies show that aspirin given with nonsteroidal anti-inflammatory agents, including MOTRIN, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-aspirin drug. Single dose bioavailability studies in normal volunteers have failed to show an effect of aspirin on ibuprofen blood levels. Correlative clinical studies have not been done.

Methotrexate: Ibuprofen, as well as other nonsteroidal anti-inflammatory drugs, probably reduces the tubular secretion of methotrexate based on *in-vitro* studies in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if MOTRIN is administered concomitantly with methotrexate.

H-2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Clinical studies, as well as random observations, have shown that ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with ibuprofen, the patient should be observed closely for signs of renal failure (See **PRECAUTIONS, Renal Effects**) as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of concomitant drug administration. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity. (Read circulars for lithium preparation before use of such concurrent therapy.)

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of MOTRIN is not recommended during pregnancy.

Nursing Mothers: In limited studies, an assay capable of detecting 1 mcg/ml did not demonstrate ibuprofen in the milk of lactating mothers. However, because of the limited nature of the studies, and the possible adverse effects of prostaglandin-inhibiting drugs on neonates, MOTRIN is not recommended for use in nursing mothers.

ADVERSE REACTIONS

The most frequent type of adverse reaction occurring with MOTRIN Tablets (ibuprofen) is gastrointestinal. In controlled clinical trials the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

In controlled studies when MOTRIN was compared to aspirin and indomethacin in equally effective doses, the overall incidence of gastrointestinal complaints was about half that seen in either the aspirin- or indomethacin-treated patients.

Adverse reactions observed during controlled clinical trials at an incidence greater than 1% are listed in the table. Those reactions listed in Column one encompass observations in approximately 3,000 patients. More than 500 of these patients were treated for periods of at least 54 weeks.

Still other reactions occurring less frequently than 1 in 100 were reported in controlled clinical trials and from marketing experience. These reactions have been divided into two categories: Column two of the following table lists reactions with therapy with MOTRIN where the probability of a causal relationship exists: for the reactions in Column three, a causal relationship with MOTRIN has not been established. Reported side effects were higher at doses of 3200 mg/day than at doses of 2400 mg or less per day in clinical trials of patients with rheumatoid arthritis. The increases in incidence were slight and still within the ranges reported in the following table.

[See table on next page].

OVERDOSAGE

Approximately 1½ hours after the reported ingestion of from 7 to 10 MOTRIN Tablets (ibuprofen) (400 mg), a 19-month old child weighing 12 kg was seen in the hospital emergency room, apneic and cyanotic, responding only to painful stimuli. This type of stimulus, however, was sufficient to induce respiration. Oxygen and parenteral fluids were given; a greenish-yellow fluid was aspirated from the stomach with no evidence to indicate the presence of ibuprofen. Two hours after ingestion the child's condition seemed stable; she still responded only to painful stimuli and continued to have periods of apnea lasting from 5 to 10 sec-

Continued on next page

Information on these Upjohn products is based on labeling in effect September 1, 1987. Further information concerning these and other Upjohn products may be obtained by direct inquiry to Medical Information, The Upjohn Company, Kalamazoo, Michigan 49001.

Upjohn—Cont.

onds. She was admitted to intensive care and sodium bicarbonate was administered as well as infusions of dextrose and normal saline. By four hours post-ingestion she could be aroused easily, sit by herself and respond to spoken commands. Blood level of ibuprofen was 102.9 μg/ml approximately 8½ hours after accidental ingestion. At 12 hours she appeared to be completely recovered.

In two other reported cases where children (each weighing approximately 10 kg) accidentally, acutely ingested approximately 120 mg/kg, there were no signs of acute intoxication or late sequelae. Blood level in one child 90 minutes after ingestion was 700 μg/ml—about 10 times the peak levels seen in absorption-excretion studies.

A 19-year old male who had taken 8,000 mg of ibuprofen over a period of a few hours complained of dizziness, and nystagmus was noted. After hospitalization, parenteral hydration and three days' bed rest, he recovered with no reported sequelae.

In cases of acute overdosage, the stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour has elapsed since ingestion. Because the drug is acidic and is excreted in the urine, it is theoretically beneficial to administer alkali and induce diuresis. In addition to supportive measures the use of oral activated charcoal may help to reduce the absorption and reabsorption of MOTRIN.

DOSAGE AND ADMINISTRATION

Do not exceed 3200 mg total daily dose. If gastrointestinal complaints occur, administer MOTRIN Tablets (ibuprofen) with meals or milk.

Rheumatoid arthritis and osteoarthritis, including flare-ups of chronic disease:

Suggested Dosage: 1200 mg-3200 mg daily (300 mg qid; 400 mg, 600 mg or 800 mg tid or qid). Individual patients may show a better response to 3200 mg daily, as compared with 2400 mg, although in well-controlled clinical trials patients on 3200 mg did not show a better mean response in terms of efficacy. Therefore, when treating patients with 3200 mg/day, the physician should observe sufficient increased clinical benefits to offset potential increased risk.

The dose should be tailored to each patient, and may be lowered or raised depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond.

In general, patients with rheumatoid arthritis seem to require higher doses of MOTRIN than do patients with osteoarthritis.

The smallest dose of MOTRIN that yields acceptable control should be employed. A linear blood level dose-response relationship exists with single doses up to 800 mg (See CLINICAL PHARMACOLOGY for effects of food on rate of absorption).

The availability of four tablet strengths facilitates dosage adjustment.

In chronic conditions, a therapeutic response to therapy with MOTRIN is sometimes seen in a few days to a week but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

Mild to moderate pain:

400 mg every 4 to 6 hours as necessary for relief of pain. In controlled analgesic clinical trials, doses of MOTRIN greater than 400 mg were no more effective than the 400 mg dose.

Dysmenorrhea:

For the treatment of dysmenorrhea, beginning with the earliest onset of such pain, MOTRIN should be given in a dose of 400 mg every 4 hours as necessary for the relief of pain.

HOW SUPPLIED

MOTRIN Tablets (ibuprofen) are supplied as follows:

MOTRIN Tablets, 300 mg (white)	
Bottles of 500	NDC 0009-0733-02
Unit of Use bottles of 60	NDC 0009-0733-01
MOTRIN Tablets, 400 mg (orange)	
Bottles of 500	NDC 0009-0750-02
Unit-dose package of 100	NDC 0009-0750-06
Unit of Use bottles of 100	NDC 0009-0750-25
MOTRIN Tablets, 600 mg (peach)	
Unit-dose package of 100	NDC 0009-0742-05
Bottles of 500	NDC 0009-0742-02
Unit of Use bottles of 100	NDC 0009-0742-03
MOTRIN Tablets, 800 mg (apricot)	
Bottles of 100	NDC 0009-0725-01
Bottles of 500	NDC 0009-0725-03
Unit-dose package of 100	NDC 0009-0725-02
Unit of Use bottles of 30	NDC 0009-0725-06
Unit of Use bottles of 50	NDC 0009-0725-07

Code 810 015 225

Shown in Product Identification Section, page 433

MYCIGUENT® Antibiotic Ointment

(See PDR For Nonprescription Drugs)

MYCITRACIN® Triple Antibiotic Ointment

(See PDR For Nonprescription Drugs)

ORINASE® ℞

brand of tolbutamide tablets, USP

0.5 gram, 100's, Unit Dose NSN 6505-00-131-9268 (M)

DESCRIPTION

ORINASE Tablets contain tolbutamide, an oral blood glucose lowering drug of the sulfonylurea category. Tolbutamide is a pure white crystalline compound practically insoluble in water but forming water-soluble salts with alkalies. The chemical names for tolbutamide are (1) Benzenesulfonamide, N-[(butylamino) carbonyl]-4-methyl; (2) 1-Butyl-3-(p-tolylsulfonyl)urea and its molecular weight is 270.35.

Each ORINASE Tablet for oral administration contains 250 mg or 500 mg tolbutamide. Inactive ingredients: **250 mg**—aluminum hydroxide, dibasic calcium phosphate, magnesium aluminum silicate, magnesium stearate; **500**

MOTRIN

Incidence Greater than 1% (but less than 3%) Probable Causal Relationship	Precise Incidence Unknown (but less than 1%) Probable Causal Relationship**	Precise Incidence Unknown (but less than 1%) Causal Relationship Unknown**
GASTROINTESTINAL		
Nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence)	Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; pancreatis	
CENTRAL NERVOUS SYSTEM		
Dizziness*, headache, nervousness	Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma	Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri
DERMATOLOGIC		
Rash* (including maculopapular type), pruritis	Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia	Toxic epidermal necrolysis, photoallergic skin reactions
SPECIAL SENSES		
Tinnitus	Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS)	Conjunctivitis, diplopia, optic neuritis, cataracts
HEMATOLOGIC	Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS)	Bleeding episodes (eg epistaxis, menorrhagia)
METABOLIC/ENDOCRINE		
Decreased appetite		Gynecomastia, hypoglycemic reaction, acidosis
CARDIOVASCULAR		
Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS)	Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations	Arrhythmias (sinus tachycardia, sinus bradycardia)
ALLERGIC	Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS)	Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema
RENAL	Acute renal failure (see PRECAUTIONS), decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria	Renal papillary necrosis
MISCELLANEOUS	Dry eyes and mouth, gingival ulcer, rhinitis	

* Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

** Reactions are classified under "*Probable Causal Relationship (PCR)*" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under "*Causal Relationship Unknown*" if seven or more events have been reported but the criteria for PCR have not been met.