PHYSICIANS' DESK REFERENCE®

Medical Consultant
Ronald Arky, MD, Charles S. Davidson Professor of Medicine and Master, Francis Weld Peabody Society, Harvard Medical School

President and Chief Operating Officer, Drug Information Services Group: Thomas F. Rice

Director of Product Management: Stephen B. Greenberg
Associate Product Managers: Cy S. Caine, Howard N. Kanter
National Sales Manager: James R. Pantaleo
Senior Account Manager: Michael S. Sarajian
Account Managers
Dikran N. Barsamian
Donald V. Bruccoleri
Lawrence C. Keary
Jeffrey M. Keller
P. Anthony Pinsonault
Anthony Sorce
Trade Sales Manager: Robin B. Bartlett
Trade Sales Account Executive: Bill Gaffney
Direct Marketing Manager: Robert W. Chapman
Marketing Communications Manager: Maryann Malorgio
Director, Professional Support Services: Mukesh Mehta, RPh
Drug Information Specialists: Thomas Fleming, RPh, Marion Gray, RPh
Editor, Special Projects: David W. Sifton

Vice President of Production: Steven R. Andreazza
Manager, Database Administration: Lynne Handler
Contracts and Support Services Director: Marjorie A. Duffy
Director of Production: Carrie Williams
Production Managers: Kimberly Hiller-Vivas, Tara L. Walsh
Production Coordinators: Amy B. Douma, Dawn B. McCall
Format Editors: Gregory J. Westley, Edna V. Berger
Index Editor: Jeffrey Schaefer
Art Associate: Joan K. Akerlind
Director of Corporate Communications: Gregory J. Thomas
Electronic Publishing Coordinator: Joanne M. Pearson
Electronic Publishing Designer: Kevin J. Leckner
Art Director: Richard A. Weinstock
Digital Photography: Shawn W. Cahill, Frank J. McElroy, III
Director, Circulation & Fulfillment: Marianne Clarke
Product Fulfillment Manager: Stephen Schweikhart

Officers of Medical Economics: President and Chief Executive Officer: Norman R. Snesil; President and Chief Operating Officer: Curtis B. Allen; Executive Vice President and Chief Financial Officer: J. Crispin Ashworth; Senior Vice President—Corporate Operations: John R. Ware; Senior Vice President—Corporate Business Development: Raymond M. Zoeller; Vice President, Information Services and Chief Information Officer: Edward J. Zecchini

ISBNs: 1-56363-152-0 and 1-56363-156-3

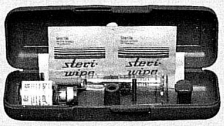
THE UPJOHN COMPANY

RX THE UPJOHN COMPANY P. 2579

305* 100 mg **170*** 50 mg

Ansaid®
(flurbiprofen)

RX THE UPJOHN COMPANY P. 2583



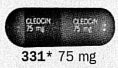
10 mcg
also available in 20 mcg

Caverject®
(alprostadil)

RX THE UPJOHN COMPANY P. 2586

395* 300 mg

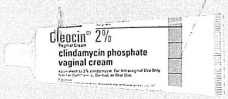
225* 150 mg



331* 75 mg

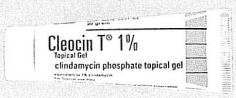
Cleocin HCl®
(clindamycin HCl)

RX THE UPJOHN COMPANY P. 2589

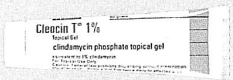


Cleocin® Vaginal Cream
(clindamycin phosphate)

RX THE UPJOHN COMPANY P. 2590



60 gram topical gel tube



30 gram topical gel tube

Cleocin T®
(clindamycin phosphate)

RX THE UPJOHN COMPANY P. 2590

60 mL bottle topical lotion

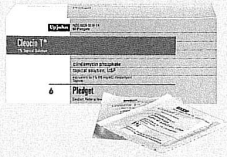
Cleocin T®
(clindamycin phosphate) 10 mg/mL

RX THE UPJOHN COMPANY P. 2590

30 mL and 60 mL bottle topical solution

Cleocin T®
(clindamycin phosphate) 10 mg/mL

RX THE UPJOHN COMPANY P. 2590



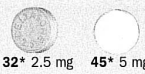
10 mg/mL topical solution
60 pledgets

Cleocin T®
(clindamycin phosphate)

RX THE UPJOHN COMPANY P. 2591

Colestid
(micronized colestipol HCl)

RX THE UPJOHN COMPANY P. 2595



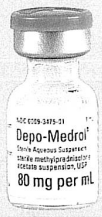
32* 2.5 mg **45*** 5 mg

193* 10 mg

165* 20 mg **388*** 50 mg

Deltasone®
(prednisone)

RX THE UPJOHN COMPANY P. 2600



Sterile aqueous suspension

Depo-Medrol®
(sterile methylprednisolone acetate, USP)

RX THE UPJOHN COMPANY P. 2607

24* 50 mg

Didrex®
(benzphetamine HCl)

RX THE UPJOHN COMPANY P. 2609

1.5 mg 3 mg

6 mg

Glynase® PresTab®
(micronized glyburide)

CIV THE UPJOHN COMPANY P. 2611

10* 0.125 mg **17***0.25 mg

Halcion®
(triazolam,USP)

C-III THE UPJOHN COMPANY P. 2614

14* 2 mg **19*** 5 mg **36*** 10 mg

Halotestin®
(fluoxymesterone)

RX THE UPJOHN COMPANY P. 2618

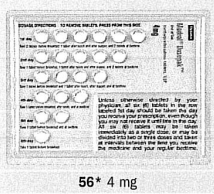
121* 2.5 mg **137*** 10 mg

Loniten®
(minoxidil)

RX THE UPJOHN COMPANY P. 2621

49* 2 mg **56*** 4 mg **22*** 8 mg

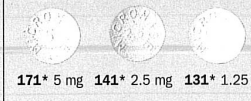
73*16 mg **155*** 24 mg **176*** 32 mg



56* 4 mg

Medrol® Dosepak™
(methylprednisolone)

RX THE UPJOHN COMPANY P. 2623

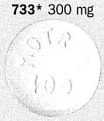


171* 5 mg **141*** 2.5 mg **131*** 1.25 mg

Micronase®
(glyburide)

RX THE UPJOHN COMPANY P. 2625

733* 300 mg



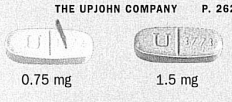
750* 400 mg

742* 600 mg

725* 800 mg

Motrin®
(ibuprofen)

RX THE UPJOHN COMPANY P. 2629



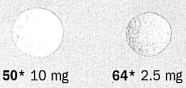
0.75 mg 1.5 mg

3 mg
tablets

vaginal cream

Ogen®
(estropipate)

RX THE UPJOHN COMPANY P. 2636



50* 10 mg **64*** 2.5 mg

286* 5 mg

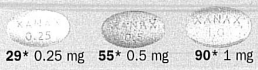
Provera®
(medroxyprogesterone acetate)

RX THE UPJOHN COMPANY P. 2637

2% per 60 mL
Topical Solution with dropper

Rogaine®
(minoxidil)

C-IV THE UPJOHN COMPANY P. 2649



29* 0.25 mg **55*** 0.5 mg **90*** 1 mg

94* 2 mg

Xanax®
(alprazolam)

UPSHER-SMITH

RX UPSHER-SMITH LABORATORIES P. 2657

600 mg (8 mEq)

750 mg (10 mEq)
Extended-release tablets, USP

Klor-Con® 8/Klor-Con® 10
(potassium chloride)

OTC UPSHER-SMITH LABORATORIES P. 2659

250 mg 500 mg

750 mg
(Tablets are scored)

Slo-Niacin®
polygel® controlled-release niacin
(nicotinic acid)

While every effort has been made to reproduce products faithfully, this section is to be considered a quick reference identification aid. In cases of suspected overdosage, etc., chemical analysis of the product should be done.

WALLACE LABORATORIES

C-IV WALLACE LABORATORIES P. 2664

7.5 mg

15 mg

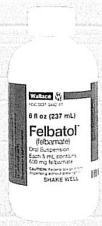
Doral®
(quazepam)

RX WALLACE LABORATORIES P. 2666

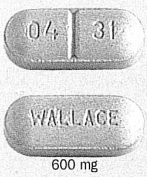
400 mg

Felbatol®
(felbamate)

RX WALLACE LABORATORIES P. 2666



600 mg/5 mL per 8 fl. oz.



600 mg

Felbatol®
(felbamate)

RX WALLACE LABORATORIES P. 2672

200 mg

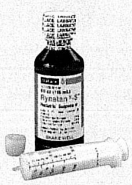
100 mg/5 mL

†Organidin® NR
(guaifenesin)

RX WALLACE LABORATORIES P. 2673

Rynatan®
(phenylephrine tannate, chlorpheniramine tannate, pyrilamine tannate)
25 mg / 8 mg / 25 mg

RX WALLACE LABORATORIES P. 2673



Rynatan®-S Pediatric Suspension
(phenylephrine tannate, chlorpheniramine tannate, pyrilamine tannate)
5 mg / 2 mg / 12.5 mg / 5 mL

RX WALLACE LABORATORIES P. 2674

350 mg

Soma®
(carisoprodol)

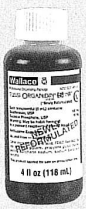
RX WALLACE LABORATORIES P. 2675

Soma® Compound
(carisoprodol, aspirin)
200 mg / 325 mg

C-III WALLACE LABORATORIES P. 2676

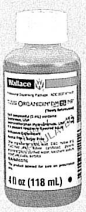
Soma® Compound w/Codeine
(carisoprodol, aspirin, codeine phosphate)
200 mg / 325 mg / 16 mg

C-V WALLACE LABORATORIES P. 2677



Tussi-Organidin®-S NR*
(guaifenesin, codeine phosphate)
100 mg / 10 mg / 5 mL
(* newly reformulated)

RX WALLACE LABORATORIES P. 2677



Tussi-Organidin® DM-S NR*
(guaifenesin, dextromethorphan HBr)
100 mg / 10 mg / 5 mL
(* newly reformulated)

WATER-JEL TECHNOLOGIES

OTC WATER-JEL TECHNOLOGIES P. 2682

Water-Jel® Burn Jel®
3-pack unit dose box
and 4 oz. bottle

OTC WATER-JEL TECHNOLOGIES P. 2682

Water-Jel® First Aid Emergency Burn Dressing
Sterile gel-soaked burn dressing
2" x 6" and 4" x 4"

WYETH-AYERST

As a result of the merger of Wyeth Laboratories and Ayerst Laboratories, all prescription products formerly of both companies are now products of Wyeth-Ayerst Laboratories. All nonprescription products formerly of Ayerst Laboratories are products of Whitehall Laboratories.

RX WYETH-AYERST LABORATORIES P. 2692

100 mg/5 mL

Children's Advil® Suspension
(ibuprofen)

RX WYETH-AYERST LABORATORIES P. 2695

809* 250 mg **810*** 500 mg

Antabuse®
(disulfiram)

C-IV WYETH-AYERST LABORATORIES P. 2700

81** 0,5 mg **64**** 1 mg **65**** 2 mg

∆Ativan®
(lorazepam)

RX WYETH-AYERST LABORATORIES P. 2701

243* 500 mg

†Atromid-S®
(clofibrate)

OTC WYETH-AYERST LABORATORIES P. 2708

1 pound Powder
Also available in Ready-to-Feed and Concentrated Liquids

Bonamil™ Infant Formula with iron

RX WYETH-AYERST LABORATORIES P. 2712

4188* 200 mg

Cordarone®
(amiodarone HCl)

RX WYETH-AYERST LABORATORIES P. 2718

702* 50 mg

Diucardin®
(hydroflumethiazide)

RX WYETH-AYERST LABORATORIES P. 2719

701** 25 mg

781** 37.5 mg

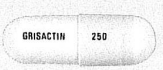
703** 50 mg

704** 75 mg

705** 100 mg

†EFFEXOR®
(venlafaxine HCl)

RX WYETH-AYERST LABORATORIES P. 2724



443* 250 mg

444* 500 mg

†Grisactin®
(griseofulvin, microsize)

RX WYETH-AYERST LABORATORIES P. 2732

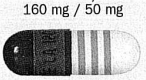
484* 40/25
40 mg / 25 mg

488* 80/25
80 mg / 25 mg

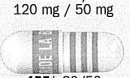
∆Inderide®
(propranolol HCl, hydrochlorothiazide)

RX WYETH-AYERST LABORATORIES P. 2734

459* 160/50
160 mg / 50 mg



457* 120/50
120 mg / 50 mg



455* 80/50
80 mg / 50 mg
Long-Acting Capsules

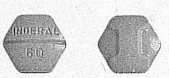
∆Inderide® LA
(propranolol HCl, hydrochlorothiazide)

RX WYETH-AYERST LABORATORIES P. 2728

421* 10 mg

422* 20 mg

424* 40 mg



426* 60 mg

428* 80 mg

3265* 1 mg/mL
Injectable

∆Inderal®
(propranolol HCl)

RX WYETH-AYERST LABORATORIES P. 2730

470* 60 mg

471* 80 mg

473* 120 mg

479*160 mg
Long-Acting Capsules

∆Inderal® LA
(propranolol HCl)

RX WYETH-AYERST LABORATORIES P. 2741

4140*
Tembids® Capsule
Controlled Release

4125* 40 mg
Tembids® Tablet
Sustained Action

†Isordil®
(isosorbide dinitrate)

† The appearance of these tablets and capsules is a trademark of Wyeth-Ayerst Laboratories. ∆ The appearance of these tablets and capsules is a registered trademark of Wyeth-Ayerst Laboratories.
** Product identification number on reverse side

Wallace Laboratories—Cont.

ment. There is no way to establish whether or not the administration of DORAL caused these events.
Hypokinesia, ataxia, confusion, incoordination, hyperkinesia, speech disorder and tremor were reported.
Also, depression, nervousness, agitation, amnesia, anorexia, anxiety, apathy, euphoria, impotence, decreased libido, paranoid reaction, nightmares, abnormal thinking, abnormal taste perception, abnormal vision, and cataract were reported.
Also reported were urinary incontinence, palpitations, nausea, constipation, diarrhea, abdominal pain, pruritus, rash, asthenia, and malaise.
The following list provides an overview of adverse experiences that have been reported and are considered to be reasonably related to the administration of benzodiazepines: incontinence, slurred speech, urinary retention, jaundice, dysarthria, dystonia, changes in libido, irritability, and menstrual irregularities.
As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations, and other adverse behavioral effects may occur in rare instances and in a random fashion. Should these occur, use of the drug should be discontinued. There have been reports of withdrawal signs and symptoms of the type associated with withdrawal from CNS depressant drugs following the rapid decrease or the abrupt discontinuation of benzodiazepines (see **Drug Abuse and Dependence** section).

DRUG ABUSE AND DEPENDENCE

Controlled Substance: DORAL is a controlled substance under the Controlled Substance Act and has been assigned by the Drug Enforcement Administration to Schedule IV.
Abuse and Dependence: Withdrawal symptoms similar in character to those noted with barbiturates and alcohol (e.g., convulsions, tremor, abdominal and muscle cramps, vomiting and sweating) have occurred following abrupt discontinuance of benzodiazepines. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving quazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

OVERDOSAGE

Manifestations of overdosage seen with other benzodiazepines include somnolence, confusion, and coma. In the event that an overdose occurs, the following is the recommended treatment. Respiration, pulse, and blood pressure should be monitored, as in all cases of drug overdosage. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be treated with the use of norepinephrine bitartrate or metaraminol bitartrate. Dialysis is of limited value. Animal experiments suggest that forced diuresis or hemodialysis are probably of little value in treating overdosage. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.
The oral LD_{50} in mice was greater than 5,000 mg/kg.

DOSAGE AND ADMINISTRATION

Adults: Initiate therapy at 15 mg until individual responses are determined. In some patients, the dose may then be reduced to 7.5 mg.
Elderly and debilitated patients: Because the elderly and debilitated may be more sensitive to benzodiazepines, attempts to reduce the nightly dosage after the first one or two nights of therapy are suggested.

HOW SUPPLIED

DORAL Tablets, 7.5 mg, unscored, capsule-shaped, light orange, slightly white speckled tablets, impressed with the product identification number 7.5 on one side of the tablet, and the product name (DORAL) on the other.

7.5 mg	Bottles of 100	NDC 0037-9000-01
	Unit-dose pkg. (10 strips of 10)	NDC 0037-9000-02

DORAL Tablets, 15 mg, unscored, capsule-shaped, light orange, slightly white speckled tablets, impressed with the product identification number 15 on one side of the tablet, and the product name (DORAL) on the other.

15 mg	Bottles of 100	NDC 0037-9002-01
	Unit-dose pkg. (10 strips of 10)	NDC 0037-9002-02

Store DORAL Tablets between 2°–30°C (36°–86°F). Protect unit doses from excessive moisture.
Distributed by
WALLACE LABORATORIES
Division of Carter-Wallace, Inc.
Cranbury, NJ 08512
Under license from Baker Cummins Pharmaceuticals, Inc.
Manufactured by Schering Corporation
Kenilworth, NJ 07033

Rev. 8/91

Shown in Product Identification Guide, page 338

FELBATOL®

℞

(felbamate)
Tablets 400 mg and 600 mg,
Oral Suspension 600 mg/5 mL

Before Prescribing FELBATOL® (felbamate), the physician should be thoroughly familiar with the details of this prescribing information.
FELBATOL® SHOULD NOT BE USED BY PATIENTS UNTIL THERE HAS BEEN A COMPLETE DISCUSSION OF THE RISKS AND THE PATIENT, PARENT, OR GUARDIAN HAS PROVIDED WRITTEN INFORMED CONSENT (SEE PATIENT INFORMATION/CONSENT SECTION).

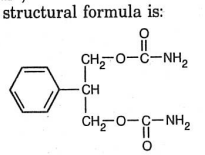
WARNING

1. APLASTIC ANEMIA
THE USE OF FELBATOL® (felbamate) IS ASSOCIATED WITH A MARKED INCREASE IN THE INCIDENCE OF APLASTIC ANEMIA. ACCORDINGLY, FELBATOL® SHOULD ONLY BE USED IN PATIENTS WHOSE EPILEPSY IS SO SEVERE THAT THE RISK OF APLASTIC ANEMIA IS DEEMED ACCEPTABLE IN LIGHT OF THE BENEFITS CONFERRED BY ITS USE (SEE **INDICATIONS**). ORDINARILY, A PATIENT SHOULD NOT BE PLACED ON AND/OR CONTINUED ON FELBATOL® WITHOUT CONSIDERATION OF APPROPRIATE EXPERT HEMATOLOGIC CONSULTATION.
AMONG FELBATOL® TREATED PATIENTS, APLASTIC ANEMIA (PANCYTOPENIA IN THE PRESENCE OF A BONE MARROW LARGELY DEPLETED OF HEMATOPOIETIC PRECURSORS) OCCURS AT AN INCIDENCE THAT MAY BE MORE THAN A 100 FOLD GREATER THAN THAT SEEN IN THE UNTREATED POPULATION (I.E., 2 TO 5 PER MILLION PERSONS PER YEAR). THE RISK OF DEATH IN PATIENTS WITH APLASTIC ANEMIA GENERALLY VARIES AS A FUNCTION OF ITS SEVERITY AND ETIOLOGY; CURRENT ESTIMATES OF THE OVERALL CASE FATALITY RATE ARE IN THE RANGE OF 20 TO 30%, BUT RATES AS HIGH AS 70% HAVE BEEN REPORTED IN THE PAST.
THERE ARE TOO FEW FELBATOL® ASSOCIATED CASES, AND TOO LITTLE KNOWN ABOUT THEM TO PROVIDE A RELIABLE ESTIMATE OF THE SYNDROME'S INCIDENCE OR ITS CASE FATALITY RATE OR TO IDENTIFY THE FACTORS, IF ANY, THAT MIGHT CONCEIVABLY BE USED TO PREDICT WHO IS AT GREATER OR LESSER RISK.
IN MANAGING PATIENTS ON FELBATOL®, IT SHOULD BE BORNE IN MIND THAT THE CLINICAL MANIFESTATION OF APLASTIC ANEMIA MAY NOT BE SEEN UNTIL AFTER A PATIENT HAS BEEN ON FELBATOL® FOR SEVERAL MONTHS (E.G., ONSET OF APLASTIC ANEMIA AMONG FELBATOL® EXPOSED PATIENTS FOR WHOM DATA ARE AVAILABLE HAS RANGED FROM 5 TO 30 WEEKS). HOWEVER, THE INJURY TO BONE MARROW STEM CELLS THAT IS HELD TO BE ULTIMATELY RESPONSIBLE FOR THE ANEMIA MAY OCCUR WEEKS TO MONTHS EARLIER. ACCORDINGLY, PATIENTS WHO ARE DISCONTINUED FROM FELBATOL® REMAIN AT RISK FOR DEVELOPING ANEMIA FOR A VARIABLE, AND UNKNOWN, PERIOD AFTERWARDS.
IT IS NOT KNOWN WHETHER OR NOT THE RISK OF DEVELOPING APLASTIC ANEMIA CHANGES WITH DURATION OF EXPOSURE. CONSEQUENTLY, IT IS NOT SAFE TO ASSUME THAT A PATIENT WHO HAS BEEN ON FELBATOL® WITHOUT SIGNS OF HEMATOLOGIC ABNORMALITY FOR LONG PERIODS OF TIME IS WITHOUT RISK.
IT IS NOT KNOWN WHETHER OR NOT THE DOSE OF FELBATOL® AFFECTS THE INCIDENCE OF APLASTIC ANEMIA.
IT IS NOT KNOWN WHETHER OR NOT CONCOMITANT USE OF ANTIEPILEPTIC DRUGS AND/OR OTHER DRUGS AFFECTS THE INCIDENCE OF APLASTIC ANEMIA.
APLASTIC ANEMIA TYPICALLY DEVELOPS WITHOUT PREMONITORY CLINICAL OR LABORATORY SIGNS, THE FULL BLOWN SYNDROME PRESENTING WITH SIGNS OF INFECTION, BLEEDING, OR ANEMIA. ACCORDINGLY, ROUTINE BLOOD TESTING CANNOT BE RELIABLY USED TO REDUCE THE INCIDENCE OF APLASTIC ANEMIA, BUT, IT WILL, IN SOME CASES, ALLOW THE DETECTION OF THE HEMATOLOGIC CHANGES BEFORE THE SYNDROME DECLARES ITSELF CLINICALLY. FELBATOL® SHOULD BE DISCONTINUED IF ANY EVIDENCE OF BONE MARROW DEPRESSION OCCURS.

2. HEPATIC FAILURE
HEPATIC FAILURE RESULTING IN FATALITIES HAS BEEN REPORTED WITH A MARKED INCREASE IN THE FREQUENCY IN PATIENTS RECEIVING FELBATOL® (felbamate). ACCORDINGLY, FELBATOL SHOULD ONLY BE USED IN PATIENTS WHOSE EPILEPSY IS SO SEVERE THAT THE RISK OF LIVER FAILURE IS OUTWEIGHED BY THE POTENTIAL BENEFITS OF SEIZURE CONTROL.
ALTHOUGH FULL INFORMATION IS NOT YET AVAILABLE, THE NUMBER OF CASES REPORTED GREATLY EXCEEDS THE NUMBER THAT IS EXPECTED BASED ON THE ANNUAL INCIDENCE OF ACUTE LIVER FAILURE IN THE UNITED STATES (I.E., ABOUT 2,000 CASES PER YEAR).
THERE ARE TOO FEW FELBATOL® ASSOCIATED CASES OF HEPATIC FAILURE AND TOO LITTLE KNOWN ABOUT THEM TO PROVIDE EITHER A RELIABLE ESTIMATE OF ITS INCIDENCE OR TO IDENTIFY THE FACTORS, IF ANY, THAT MIGHT BE USED TO PREDICT WHICH PATIENT IS AT GREATER OR LESSER RISK.
IT IS NOT KNOWN WHETHER OR NOT THE RISK OF DEVELOPING HEPATIC FAILURE CHANGES WITH DURATION OF EXPOSURE.
IT IS NOT KNOWN WHETHER OR NOT THE DOSAGE OF FELBATOL® AFFECTS THE INCIDENCE OF HEPATIC FAILURE.
IT IS NOT KNOWN WHETHER CONCOMITANT USE OF OTHER ANTIEPILEPTIC DRUGS AND/OR OTHER DRUGS AFFECTS THE INCIDENCE OF HEPATIC FAILURE.
FELBATOL® SHOULD NOT BE PRESCRIBED FOR ANYONE WITH A HISTORY OF HEPATIC DYSFUNCTION.
PATIENTS PRESCRIBED FELBATOL® SHOULD HAVE LIVER FUNCTION TESTS (AST, ALT, BILIRUBIN) PERFORMED BEFORE INITIATING FELBATOL® AND AT 1- TO 2-WEEK INTERVALS WHILE TREATMENT CONTINUES. A PATIENT WHO DEVELOPS ABNORMAL LIVER FUNCTION TESTS SHOULD BE IMMEDIATELY WITHDRAWN FROM FELBATOL® TREATMENT.

DESCRIPTION

FELBATOL® (felbamate) is an antiepileptic available as 400 mg and 600 mg tablets and as a 600 mg/5 mL suspension for oral administration. Its chemical name is 2-phenyl-1,3-propanediol dicarbamate.
Felbamate is a white to off-white crystalline powder with a characteristic odor. It is very slightly soluble in water, slightly soluble in ethanol, sparingly soluble in methanol, and freely soluble in dimethyl sulfoxide. The molecular weight is 238.24; felbamate's molecular formula is $C_{11}H_{14}N_2O_4$; its structural formula is:



The inactive ingredients for FELBATOL® (felbamate) tablets 400 mg and 600 mg are starch, microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, FD&C Yellow No. 6, D&C Yellow No. 10, and FD&C Red No. 40 (600 mg tablets only). The inactive ingredients for FELBATOL® (felbamate) suspension 600 mg/5 mL are sorbitol, glycerin, microcrystalline cellulose, carboxymethylcellulose sodium, simethicone, polysorbate 80, methylparaben, saccharin sodium, propylparaben, FD&C Yellow No. 6, FD&C Red No. 40, flavorings, and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action:
The mechanism by which felbamate exerts its anticonvulsant activity is unknown, but in animal test systems designed to detect anticonvulsant activity, felbamate has properties in common with other marketed anticonvulsants.

Felbamate is effective in mice and rats in the maximal electroshock test, the subcutaneous pentylenetetrazol seizure test, and the subcutaneous picrotoxin seizure test. Felbamate also exhibits anticonvulsant activity against seizures induced by intracerebroventricular administration of glutamate in rats and N-methyl-D,L-aspartic acid in mice. Protection against maximal electroshock-induced seizures suggests that felbamate may reduce seizure spread, an effect possibly predictive of efficacy in generalized tonic-clonic or partial seizures. Protection against pentylenetetrazol-induced seizures suggests that felbamate may increase seizure threshold, an effect considered to be predictive of potential efficacy in absence seizures.

Receptor-binding studies *in vitro* indicate that felbamate has weak inhibitory effects on GABA-receptor binding, benzodiazepine receptor binding, and is devoid of activity at the MK-801 receptor binding site of the NMDA receptor-ionophore complex. However, felbamate does interact as an antagonist at the strychnine-insensitive glycine recognition site of the NMDA receptor-ionophore complex. Felbamate is not effective in protecting chick embryo retina tissue against the neurotoxic effects of the excitatory amino acid agonists NMDA, kainate, or quisqualate *in vitro*.

The monocarbamate, p-hydroxy, and 2-hydroxy metabolites were inactive in the maximal electroshock-induced seizure test in mice. The monocarbamate and p-hydroxy metabolites had only weak (0.2 to 0.6) activity compared with felbamate in the subcutaneous pentylenetetrazol seizure test. These metabolites did not contribute significantly to the anticonvulsant action of felbamate.

Pharmacokinetics:

The numbers in the pharmacokinetic section are mean ± standard deviation.

Felbamate is well-absorbed after oral administration. Over 90% of the radioactivity after a dose of 1000 mg ^{14}C felbamate was found in the urine. Absolute bioavailability (oral vs. parenteral) has not been measured. The tablet and suspension were each shown to be bioequivalent to the capsule used in clinical trials, and pharmacokinetic parameters of the tablet and suspension are similar. There was no effect of food on absorption of the tablet; the effect of food on absorption of the suspension has not been evaluated.

Following oral administration, felbamate is the predominant plasma species (about 90% of plasma radioactivity). About 40–50% of absorbed dose appears unchanged in urine, and an additional 40% is present as unidentified metabolites and conjugates. About 15% is present as parahydroxyfelbamate, 2-hydroxyfelbamate, and felbamate monocarbamate, none of which have significant anticonvulsant activity.

Binding of felbamate to human plasma protein was independent of felbamate concentrations between 10 and 310 micrograms/mL. Binding ranged from 22% to 25%, mostly to albumin, and was dependent on the albumin concentration.

Felbamate is excreted with a terminal half-life of 20–23 hours, which is unaltered after multiple doses. Clearance after a single 1200 mg dose is 26±3 mL/hr/kg, and after multiple daily doses of 3600 mg is 30±8 mL/hr/kg. The apparent volume of distribution was 756±82 mL/kg after a 1200 mg dose. Felbamate Cmax and AUC are proportionate to dose after single and multiple doses over a range of 100–800 mg single doses and 1200–3600 mg daily doses. Cmin (trough) blood levels are also dose proportional. Multiple daily doses of 1200, 2400, and 3600 mg gave Cmin values of 30±5, 55±8, and 83±21 micrograms/mL (N=10 patients). Felbamate gave dose proportional steady-state peak plasma concentrations in children age 4–12 over a range of 15, 30, and 45 mg/kg/day with peak concentrations of 17, 32, and 49 micrograms/mL.

The effects of race and gender on felbamate pharmacokinetics have not been systematically evaluated, but plasma concentrations in males (N=5) and females (N=4) given felbamate have been similar. The effects of felbamate kinetics on renal and hepatic functional impairment have not been evaluated.

Pharmacodynamics:

Typical Physiologic Responses:

1. Cardiovascular:

In adults, there is no effect of felbamate on blood pressure. Small but statistically significant mean increases in heart rate were seen during adjunctive therapy and monotherapy; however, these mean increases of up to 5 bpm were not clinically significant. In children, no clinically relevant changes in blood pressure or heart rate were seen during adjunctive therapy or monotherapy with felbamate.

2. Other Physiologic Effects:

The only other change in vital signs was a mean decrease of approximately 1 respiration per minute in respiratory rate during adjunctive therapy in children. In adults, statistically significant mean reductions in body weight were observed during felbamate monotherapy and adjunctive therapy. In children, there were mean decreases in body weight during adjunctive therapy and monotherapy; however, these mean changes were not statistically significant. These mean reductions in adults and children were approximately 5% of the mean weights at baseline.

CLINICAL STUDIES

The results of controlled clinical trials established the efficacy of FELBATOL® (felbamate) as monotherapy and adjunctive therapy in adults with partial-onset seizures with or without secondary generalization and in partial and generalized seizures associated with Lennox-Gastaut syndrome in children.

FELBATOL® Monotherapy Trials in Adults

FELBATOL® (3600 mg/day given QID) and low-dose valproate (15 mg/kg/day) were compared as monotherapy during a 112-day treatment period in a multicenter and a single-center double-blind efficacy trial. Both trials were conducted according to an identical study design. During a 56-day baseline period, all patients had at least four partial-onset seizures per 28 days and were receiving one antiepileptic drug at a therapeutic level, the most common being carbamazepine. In the multicenter trial, baseline seizure frequencies were 12.4 per 28 days in the FELBATOL® group and 21.3 per 28 days in the low-dose valproate group. In the single-center trial, baseline seizure frequencies were 18.1 per 28 days in the FELBATOL® group and 15.9 per 28 days in the low-dose valproate group. Patients were converted to monotherapy with FELBATOL® or low-dose valproic acid during the first 28 days of the 112-day treatment period. Study endpoints were completion of 112 study days or fulfilling an escape criterion. Criteria for escape relative to baseline were: (1) twofold increase in monthly seizure frequency, (2) twofold increase in highest 2-day seizure frequency, (3) single generalized tonic-clonic seizure (GTC) if none occurred during baseline, or (4) significant prolongation of GTCs. The primary efficacy variable was the number of patients in each treatment group who met escape criteria.

In the multicenter trial, the percentage of patients who met escape criteria was 40% (18/45) in the Felbatol® group and 78% (39/50) in the low-dose valproate group. In the single-center trial, the percentage of patients who met escape criteria was 14% (3/21) in the Felbatol® group and 90% (19/21) in the low-dose valproate group. In both trials, the difference in the percentage of patients meeting escape criteria was statistically significant ($P < .001$) in favor of Felbatol®. These two studies by design were intended to demonstrate the effectiveness of Felbatol® monotherapy. The studies were not designed or intended to demonstrate comparative efficacy of the two drugs. For example, valproate was not used at the maximally effective dose.

Felbatol® Adjunctive Therapy Trials in Adults

A double-blind, placebo-controlled crossover trial consisted of two 10-week outpatient treatment periods. Patients with refractory partial-onset seizures who were receiving phenytoin and carbamazepine at therapeutic levels were administered Felbatol® (felbamate) as add-on therapy at a starting dosage of 1400 mg/day in three divided doses, which was increased to 2600 mg/day in three divided doses. Among the 56 patients who completed the study, the baseline seizure frequency was 20 per month. Patients treated with Felbatol® had fewer seizures than patients treated with placebo for each treatment sequence. There was a 23% ($P = .018$) difference in percentage seizure frequency reduction in favor of Felbatol®.

Felbatol® 3600 mg/day given QID and placebo were compared in a 28-day double-blind add-on trial in patients who had their standard antiepileptic drugs reduced while undergoing evaluations for surgery of intractable epilepsy. All patients had confirmed partial-onset seizures with or without generalization, seizure frequency during surgical evaluation not exceeding an average of four partial seizures per day or more than one generalized seizure per day, and a minimum average of one partial or generalized tonic-clonic seizure per day for the last 3 days of the surgical evaluation. The primary efficacy variable was time to fourth seizure after randomization to treatment with Felbatol® or placebo. Thirteen (46%) of 28 patients in the Felbatol® group versus 29 (88%) of 33 patients in the placebo group experienced a fourth seizure. The median times to fourth seizure were greater than 28 days in the Felbatol® group and 5 days in the placebo group. The difference between Felbatol® and placebo in time to fourth seizure was statistically significant ($P = .002$) in favor of Felbatol®.

Felbatol® Adjunctive Therapy Trial in Children with Lennox-Gastaut Syndrome

In a 70-day double-blind, placebo-controlled add-on trial in the Lennox-Gastaut syndrome, Felbatol® 45 mg/kg/day given QID was superior to placebo in controlling the multiple seizure types associated with this condition. Patients had at least 90 atonic and/or atypical absence seizures per month while receiving therapeutic dosages of one or two other antiepileptic drugs. Patients had a past history of using an average of eight antiepileptic drugs. The most commonly used antiepileptic drug during the baseline period was valproic acid. The frequency of all types of seizures during the baseline period was 1617 per month in the Felbatol® group and 716 per month in the placebo group. Statistically significant differences in the effect on seizure frequency favored Felbatol® over placebo for total seizures (26% reduction vs 5% increase, $P < .001$), atonic seizures (44% reduction vs 7% reduction, $P = .002$), and generalized tonic-clonic seizures (40% reduction vs 12% increase, $P = .017$). Parent/guardian global evaluations based on impressions of quality of life with respect to alertness, verbal responsiveness, general well-being, and seizure control significantly ($P < .001$) favored Felbatol® over placebo.

When efficacy was analyzed by gender in four well-controlled trials of felbamate as adjunctive and monotherapy for partial-onset seizures and Lennox-Gastaut syndrome, a similar response was seen in 122 males and 142 females.

INDICATIONS AND USAGE

Felbatol® is not indicated as a first line antiepileptic treatment (see **Warnings**). Felbatol® is recommended for use only in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use.

If these criteria are met and the patient has been fully advised of the risk and has provided written, informed consent, Felbatol® can be considered for either monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy and as adjunctive therapy in the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children.

CONTRAINDICATIONS

Felbatol® is contraindicated in patients with known hypersensitivity to Felbatol®, its ingredients, or known sensitivity to other carbamates. It should not be used in patients with a history of any blood dyscrasia or hepatic dysfunction.

WARNINGS

See Boxed Warning regarding aplastic anemia and hepatic failure.

Antiepileptic drugs should not be suddenly discontinued because of the possibility of increasing seizure frequency.

PRECAUTIONS

Information for Patients: Patients should be informed that the use of Felbatol® is associated with aplastic anemia and hepatic failure, potentially fatal conditions acutely or over a long term.

The physician should obtain written, informed consent prior to initiation of Felbatol® therapy (see **PATIENT INFORMATION/CONSENT** section).

Aplastic anemia in the general population is relatively rare. The absolute risk for the individual patient is not known with any degree of reliability, but patients on Felbatol® may be at more than a 100 fold greater risk for developing the syndrome than the general population.

The long term outlook for patients with aplastic anemia is variable. Although many patients are apparently cured, others require repeated transfusions and other treatments for relapses, and some, although surviving for years, ultimately develop serious complications that sometimes prove fatal (e.g., leukemia).

At present there is no way to predict who is likely to get aplastic anemia, nor is there a documented effective means to monitor the patient so as to avoid and/or reduce the risk. Patients with a history of any blood dyscrasia should not receive Felbatol®.

Patients should be advised to be alert for signs of infection, bleeding, easy bruising, or signs of anemia (fatigue, weakness, lassitude, etc.), and should be advised to report to the physician immediately if any such signs or symptoms appear.

Hepatic failure in the general population is relatively rare. The absolute risk for an individual patient is not known with any degree of reliability but patients on Felbatol® are at a greater risk for developing hepatic failure than the general population.

At present, there is no way to predict who is likely to develop hepatic failure, however, patients with a history of hepatic dysfunction should not be started on Felbatol®.

Patients should be advised to follow their physician's directives for liver function testing both before starting Felbatol® (felbamate) and at frequent intervals while taking Felbatol®.

Laboratory Tests: Full hematologic evaluations should be performed before Felbatol® therapy, frequently during therapy, and for a significant period of time after discontinuation of Felbatol® therapy. While it might appear prudent to perform frequent CBCs in patients continuing on Felbatol®, there is no evidence that such monitoring will allow early detection of marrow suppression before aplastic anemia occurs. (See **Boxed Warnings**). Complete pretreatment blood counts, including platelets and reticulocytes should be obtained as a baseline. If any hematologic abnormalities are detected during the course of treatment, immediate consultation with a hematologist is advised. Felbatol® should be discontinued if any evidence of bone marrow depression occurs.

Continued on next page

Wallace Laboratories—Cont.

Liver function testing (AST, ALT, bilirubin) should be done before Felbatol® is started and at 1- to 2-week intervals while the patient is taking Felbatol®. If any liver abnormalities are detected during the course of treatment, Felbatol® should be discontinued immediately. (see **PATIENT INFORMATION/CONSENT).**

Drug Interactions:

The drug interaction data described in this section were obtained from controlled clinical trials and studies involving otherwise healthy adults with epilepsy.

Use in Conjunction with Other Antiepileptic Drugs (See DOSAGE AND ADMINISTRATION):

The addition of Felbatol® to antiepileptic drugs (AEDs) affects the steady-state plasma concentrations of AEDs. The net effect of these interactions is summarized in the following table:

AED Coadministered	AED Concentration	Felbatol® Concentration
Phenytoin	↑	↓
Valproate	↑	↔**
Carbamazepine (CBZ)	↓	↓
*CBZ epoxide	↑	

* Not administered, but an active metabolite of carbamazepine.
** No significant effect.

Specific Effects of Felbatol® on Other Antiepileptic Drugs:

Phenytoin: Felbatol® causes an increase in steady-state phenytoin plasma concentrations. In 10 otherwise healthy subjects with epilepsy ingesting phenytoin, the steady-state trough (Cmin) phenytoin plasma concentration was 17±5 micrograms/mL. The steady-state Cmin increased to 21±5 micrograms/mL when 1200 mg/day of felbamate was coadministered. Increasing the felbamate dose to 1800 mg/day in six of these subjects increased the steady-state phenytoin Cmin to 25±7 micrograms/mL. In order to maintain phenytoin levels, limit adverse experiences, and achieve the felbamate dose of 3600 mg/day, a phenytoin dose reduction of approximately 40% was necessary for eight of these 10 subjects.

In a controlled clinical trial, a 20% reduction of the phenytoin dose at the initiation of Felbatol® therapy resulted in phenytoin levels comparable to those prior to Felbatol® administration.

Carbamazepine: Felbatol® causes a decrease in the steady-state carbamazepine plasma concentrations and an increase in the steady-state carbamazepine epoxide plasma concentration. In nine otherwise healthy subjects with epilepsy ingesting carbamazepine, the steady-state trough (Cmin) carbamazepine concentration was 8±2 micrograms/mL. The carbamazepine steady-state Cmin decreased 31% to 5±1 micrograms/mL when felbamate (3000 mg/day, divided into three doses) was coadministered. Carbamazepine epoxide steady-state Cmin concentrations increased 57% from 1.0±0.3 to 1.6±0.4 micrograms/mL with the addition of felbamate.

In clinical trials, similar changes in carbamazepine and carbamazepine epoxide were seen.

Valproate: Felbatol® causes an increase in steady-state valproate concentrations. In four subjects with epilepsy ingesting valproate, the steady-state trough (Cmin) valproate plasma concentration was 63±16 micrograms/mL. The steady-state Cmin increased to 78±14 micrograms/mL when 1200 mg/day of felbamate was coadministered. Increasing the felbamate dose to 2400 mg/day increased the steady-state valproate Cmin to 96±25 micrograms/mL. Corresponding values for free valproate Cmin concentrations were 7±3, 9±4, and 11±6 micrograms/mL for 0, 1200, and 2400 mg/day Felbatol®, respectively. The ratios of the AUCs of unbound valproate to the AUCs of the total valproate were 11.1%, 13.0%, and 11.5%, with coadministration of 0, 1200, and 2400 mg/day of Felbatol®, respectively. This indicates that the protein binding of valproate did not change appreciably with increasing doses of Felbatol®.

Effects of Other Antiepileptic Drugs on Felbatol®:

Phenytoin: Phenytoin causes an approximate doubling of the clearance of Felbatol® (felbamate) at steady state and, therefore, the addition of phenytoin causes an approximate 45% decrease in the steady-state trough concentrations of Felbatol® as compared to the same dose of Felbatol® given as monotherapy.

Carbamazepine: Carbamazepine causes an approximate 50% increase in the clearance of Felbatol® at steady state and, therefore, the addition of carbamazepine results in an approximate 40% decrease in the steady-state trough concentrations of Felbatol® as compared to the same dose of Felbatol® given as monotherapy.

Valproate: Available data suggest that there is no significant effect of valproate on the clearance of Felbatol® at steady state. Therefore, the addition of valproate is not expected to cause a clinically important effect on Felbatol® (felbamate) plasma concentrations.

Effects of Antacids on Felbatol®:

The rate and extent of absorption of a 2400 mg dose of Felbatol® as monotherapy given as tablets was not affected when coadministered with antacids.

Drug/Laboratory Test Interactions: There are no known interactions of Felbatol® with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies were conducted in mice and rats. Mice received felbamate as a feed admixture for 92 weeks at doses of 300, 600, and 1200 mg/kg and rats were also dosed by feed admixture for 104 weeks at doses of 30, 100, and 300 (males) or 10, 30, and 100 (females) mg/kg. The maximum doses in these studies produced steady-state plasma concentrations that were equal to or less than the steady-state plasma concentrations in epileptic patients receiving 3600 mg/day. There was a statistically significant increase in hepatic cell adenomas in high-dose male and female mice and in high-dose female rats. Hepatic hypertrophy was significantly increased in a dose-related manner in mice, primarily males, but also in females. Hepatic hypertrophy was not found in female rats. The relationship between the occurrence of benign hepatocellular adenomas and the finding of liver hypertrophy resulting from liver enzyme induction has not been examined. There was a statistically significant increase in benign interstitial cell tumors of the testes in high-dose male rats receiving felbamate. The relevance of these findings to humans is unknown.

As a result of the synthesis process, felbamate could contain small amounts of two known animal carcinogens, the genotoxic compound ethyl carbamate (urethane) and the non-genotoxic compound methyl carbamate. It is theoretically possible that a 50 kg patient receiving 3600 mg of felbamate could be exposed to up to 0.72 micrograms of urethane and 1800 micrograms of methyl carbamate. These daily doses are approximately 1/35,000 (urethane) and 1/5,500 (methyl carbamate) on a mg/kg basis, and 1/10,000 (urethane) and 1/1,600 (methyl carbamate) on a mg/m^2 basis, of the dose levels shown to be carcinogenic in rodents. Any presence of these two compounds in felbamate used in the lifetime carcinogenicity studies was inadequate to cause tumors.

Microbial and mammalian cell assays revealed no evidence of mutagenesis in the Ames *Salmonella*/microsome plate test, CHO/HGPRT mammalian cell forward gene mutation assay, sister chromatid exchange assay in CHO cells, and bone marrow cytogenetics assay.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 13.9 times the human total daily dose of 3600 mg on a mg/kg basis, or up to 3 times the human total daily dose on a mg/m^2 basis.

Pregnancy: Pregnancy Category C. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given doses up to 13.9 times (rat) and 4.2 times (rabbit) the human daily dose on a mg/kg basis, or 3 times (rat) and less than 2 times (rabbit) the human daily dose on a mg/m^2 basis. However, in rats, there was a decrease in pup weight and an increase in pup deaths during lactation. The cause for these deaths is not known. The no effect dose for rat pup mortality was 6.9 times the human dose on a mg/kg basis or 1.5 times the human dose on a mg/m^2 basis.

Placental transfer of felbamate occurs in rat pups. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of felbamate on labor and delivery in humans is unknown.

Nursing Mothers: Felbamate has been detected in human milk. The effect on the nursing infant is unknown (see **Pregnancy** section).

Pediatric Use: The safety and effectiveness of Felbatol® in children other than those with Lennox-Gastaut syndrome has not been established.

Geriatric Use: No systematic studies in geriatric patients have been conducted. Clinical studies of Felbatol® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dosage selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The most common adverse reactions seen in association with Felbatol® (felbamate) in adults during monotherapy are anorexia, vomiting, insomnia, nausea, and headache. The most common adverse reactions seen in association with Felbatol® in adults during adjunctive therapy are anorexia, vomiting, insomnia, nausea, dizziness, somnolence and headache.

The most common adverse reactions seen in association with Felbatol® in children during adjunctive therapy are anorexia, vomiting, insomnia, headache, and somnolence.

The dropout rate because of adverse experiences or intercurrent illnesses among adult felbamate patients was 12 percent (120/977). The dropout rate because of adverse experiences or intercurrent illnesses among pediatric felbamate patients was six percent (22/357). In adults, the body systems associated with causing these withdrawals in order of frequency were: digestive (4.3%), psychological (2.2%), whole body (1.7%), neurological (1.5%), and dermatological (1.5%). In children, the body systems associated with causing these withdrawals in order of frequency were: digestive (1.7%), neurological (1.4%), dermatological (1.4%), psychological (1.1%), and whole body (1.0%). In adults, specific events with an incidence of 1% or greater associated with causing these withdrawals, in order of frequency were: anorexia (1.6%), nausea (1.4%), rash (1.2%), and weight decrease (1.1%). In children, specific events with an incidence of 1% or greater associated with causing these withdrawals, in order of frequency was rash (1.1%).

Incidence in Clinical Trials:

The prescriber should be aware that the figures cited in the following table cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different investigators, treatments, and uses including the use of Felbatol® (felbamate) as adjunctive therapy where the incidence of adverse events may be higher due to drug interactions. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Adults

Incidence in Controlled Clinical Trials—Monotherapy Studies in Adults:

The table that follows enumerates adverse events that occurred at an incidence of 2% or more among 58 adult patients who received Felbatol® monotherapy at dosages of 3600 mg/day in double-blind controlled trials. Reported adverse events were classified using standard WHO-based dictionary terminology.

Adults
Treatment-Emergent Adverse Event
Incidence in Controlled Monotherapy Trials

Body System/Event	Felbatol®* (N=58) %	Low Dose Valproate** (N=50) %
Body as a Whole		
Fatigue	6.9	4.0
Weight Decrease	3.4	0
Face Edema	3.4	0
Central Nervous System		
Insomnia	8.6	4.0
Headache	6.9	18.0
Anxiety	5.2	2.0
Dermatological		
Acne	3.4	0
Rash	3.4	0
Digestive		
Dyspepsia	8.6	2.0
Vomiting	8.6	2.0
Constipation	6.9	2.0
Diarrhea	5.2	0
SGPT Increased	5.2	2.0
Metabolic/Nutritional		
Hypophosphatemia	3.4	0
Respiratory		
Upper Respiratory Tract Infection	8.6	4.0
Rhinitis	6.9	0
Special Senses		
Diplopia	3.4	4.0
Otitis Media	3.4	0
Urogenital		
Intramenstrual Bleeding	3.4	0
Urinary Tract Infection	3.4	2.0

*3600 mg/day; **15 mg/kg/day

Incidence in Controlled Add-On Clinical Studies in Adults:

The table that follows enumerates adverse events that occurred at an incidence of 2% or more among 114 adult patients who received Felbatol® adjunctive therapy in add-

on controlled trials at dosages up to 3600 mg/day. Reported adverse events were classified using standard WHO-based dictionary terminology.

Many adverse experiences that occurred during adjunctive therapy may be a result of drug interactions. Adverse experiences during adjunctive therapy typically resolved with conversion to monotherapy, or with adjustment of the dosage of other antiepileptic drugs.

Adults
Treatment-Emergent Adverse Event
Incidence in Controlled Add-On Trials

Body System/Event	Felbatol® (N=114) %	Placebo (N=43) %
Body as a Whole		
Fatigue	16.8	7.0
Fever	2.6	4.7
Chest Pain	2.6	0
Central Nervous System		
Headache	36.8	9.3
Somnolence	19.3	7.0
Dizziness	18.4	14.0
Insomnia	17.5	7.0
Nervousness	7.0	2.3
Tremor	6.1	2.3
Anxiety	5.3	4.7
Gait Abnormal	5.3	0
Depression	5.3	0
Paraesthesia	3.5	2.3
Ataxia	3.5	0
Mouth Dry	2.6	0
Stupor	2.6	0
Dermatological		
Rash	3.5	4.7
Digestive		
Nausea	34.2	2.3
Anorexia	19.3	2.3
Vomiting	16.7	4.7
Dyspepsia	12.3	7.0
Constipation	11.4	2.3
Diarrhea	5.3	2.3
Abdominal Pain	5.3	0
SGPT Increased	3.5	0
Musculoskeletal		
Myalgia	2.6	0
Respiratory		
Upper Respiratory Tract Infection	5.3	7.0
Sinusitis	3.5	0
Pharyngitis	2.6	0
Special Senses		
Diplopia	6.1	0
Taste Perversion	6.1	0
Vision Abnormal	5.3	2.3

Children

Incidence in a Controlled Add-On Trial in Children with Lennox-Gastaut Syndrome:

The table that follows enumerates adverse events that occurred more than once among 31 pediatric patients who received Felbatol® up to 45 mg/kg/day or a maximum of 3600 mg/day. Reported adverse events were classified using standard WHO-based dictionary terminology.

Children
Treatment-Emergent Adverse Event
Incidence in a Controlled Add-On Lennox-Gastaut Trial

Body System/Event	Felbatol® (N=31) %	Placebo (N=27) %
Body as a Whole		
Fever	22.6	11.1
Fatigue	9.7	3.7
Weight Decrease	6.5	0
Pain	6.5	0
Central Nervous System		
Somnolence	48.4	11.1
Insomnia	16.1	14.8
Nervousness	16.1	18.5
Gait Abnormal	9.7	0
Headache	6.5	18.5
Thinking Abnormal	6.5	3.7
Ataxia	6.5	3.7
Urinary Incontinence	6.5	7.4
Emotional Lability	6.5	0
Miosis	6.5	0
Dermatological		
Rash	9.7	7.4
Digestive		
Anorexia	54.8	14.8
Vomiting	38.7	14.8
Constipation	12.9	0
Hiccup	9.7	3.7
Nausea	6.5	0
Dyspepsia	6.5	3.7
Hematologic		
Purpura	12.9	7.4
Leukopenia	6.5	0
Respiratory		
Upper Respiratory Tract Infection	45.2	25.9
Pharyngitis	9.7	3.7
Coughing	6.5	0
Special Senses		
Otitis Media	9.7	0

Other Events Observed in Association with the Administration of Felbatol® (felbamate):

In the paragraphs that follow, the adverse clinical events, other than those in the preceding tables, that occurred in a total of 977 adults and 357 children exposed to Felbatol® (felbamate) and that are reasonably associated with its use are presented. They are listed in order of decreasing frequency. Because the reports cite events observed in open-label and uncontrolled studies, the role of Felbatol® in their causation cannot be reliably determined.

Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100–1/1000 patients; and rare events are those occurring in fewer than 1/1000 patients.

Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (N = 1334) exposed to Felbatol®.

Body as a Whole: *Frequent:* Weight increase, asthenia, malaise, influenza-like symptoms; *Rare:* anaphylactoid reaction, chest pain substernal.

Cardiovascular: *Frequent:* Palpitation, tachycardia; *Rare:* supraventricular tachycardia.

Central Nervous System: *Frequent:* Agitation, psychological disturbance, aggressive reaction; *Infrequent:* hallucination, euphoria, suicide attempt, migraine.

Digestive: *Frequent:* SGOT increased; *Infrequent:* esophagitis, appetite increased; *Rare:* GGT elevated.

Hematologic: *Infrequent:* Lymphadenopathy, leukopenia, leukocytosis, thrombocytopenia, granulocytopenia; *Rare:* antinuclear factor test positive, qualitative platelet disorder, agranulocytosis.

Metabolic/Nutritional: *Infrequent:* Hypokalemia, hyponatremia, LDH increased, alkaline phosphatase increased, hypophosphatemia; *Rare:* creatinine phosphokinase increased.

Musculoskeletal: *Infrequent:* Dystonia.

Dermatological: *Frequent:* Pruritus; *Infrequent:* urticaria, bullous eruption; *Rare:* buccal mucous membrane swelling, Stevens-Johnson Syndrome.

Special Senses: *Rare:* Photosensitivity allergic reaction.

Postmarketing Adverse Event Reports:

Voluntary reports of adverse events in patients taking Felbatol® (usually in conjunction with other drugs) have been received since market introduction and may have no causal relationship with the drug(s). These include the following by body system:

Body as a Whole: neoplasm, sepsis, placental disorder, L.E. syndrome, SIDS, sudden death, fetal death, edema, hypothermia, rigors, microcephaly.

Cardiovascular: atrial fibrillation, atrial arrhythmia, cardiac arrest, torsade de pointes, cardiac failure, hypotension, hypertension, flushing, thrombophlebitis, ischemic necrosis, gangrene, peripheral ischemia.

Central & Peripheral Nervous System: delusion, paralysis, mononeuritis, cerebrovascular disorder, cerebral edema, coma, manic reaction, encephalopathy, paranoid reaction, nystagmus, choreoathetosis, extraphyradmidal disorder, confusion, psychosis, status epilepticus, dyskinesia, dysarthria, respiratory depression.

Dermatological: abnormal body odor, sweating, lichen planus, livedo reticularis, alopecia, toxic epidermal necrolysis.

Digestive: (Refer to **WARNINGS**) hepatitis, hepatic failure, G.I. hemorrhage, hyperammonemia, pancreatitis, hematemesis, gastritis, esophagitis, rectal hemorrhage, flatulence, gingival bleeding, acquired megacolon, ileus, intestinal obstruction, enteritis, ulcerative stomatitis, glossitis, dysphagia, jaundice.

Hematologic: (Refer to **WARNINGS**) increased and decreased prothrombin time, anemia, hypochromic anemia, aplastic anemia, pancytopenia, hemolytic uremic syndrome.

Metabolic/Nutritional: hypernatremia, hypoglycemia, SIADH, hypomagnesemia, dehydration.

Musculoskeletal: arthralgia, muscle weakness, involuntary muscle contraction, rhabdomyolysis.

Respiratory: dyspnea, pneumonia, pneumonitis, hypoxia, epistaxis, pleural effusion, respiratory insufficiency, pulmonary hemorrhage.

Special Senses: hemianopsia, decreased hearing, conjunctivitis.

Urogenital: genital malformation, menstrual disorder, acute renal failure, hepatorenal syndrome, hematuria, urinary retention, nephrosis, vaginal hemorrhage.

DRUG ABUSE AND DEPENDENCE

Abuse: Abuse potential was not evaluated in human studies.

Dependence: Rats administered felbamate orally at doses 8.3 times the recommended human dose 6 days each week for 5 consecutive weeks demonstrated no signs of physical dependence as measured by weight loss following drug withdrawal on day 7 of each week.

OVERDOSAGE

Four subjects inadvertently received Felbatol® (felbamate) as adjunctive therapy in dosages ranging from 5400 to 7200 mg/day for durations between 6 and 51 days. One subject who received 5400 mg/day as monotherapy for 1 week reported no adverse experiences. Another subject attempted suicide by ingesting 12,000 mg of Felbatol® in a 12-hour period. The only adverse experiences reported were mild gastric distress and a resting heart rate of 100 bpm. No serious adverse reactions have been reported.

General supportive measures should be employed if overdosage occurs. It is not known if felbamate is dialyzable.

DOSAGE AND ADMINISTRATION

Felbatol® (felbamate) has been studied as monotherapy and adjunctive therapy in adults and as adjunctive therapy in children with seizures associated with Lennox-Gastaut syndrome. As Felbatol® is added to or substituted for existing AEDs, it is strongly recommended to reduce the dosage of those AEDs in the range of 20–33% to minimize side effects (see **Drug Interactions** subsection).

Adults (14 years of age and over)

The majority of patients received 3600 mg/day in clinical trials evaluating its use as both monotherapy and adjunctive therapy.

Monotherapy: (Initial therapy) Felbatol® (felbamate) has not been systematically evaluated as initial monotherapy. Initiate Felbatol® at 1200 mg/day in divided doses three or four times daily. The prescriber is advised to titrate previously untreated patients under close clinical supervision, increasing the dosage in 600-mg increments every 2 weeks to 2400 mg/day based on clinical response and thereafter to 3600 mg/day if clinically indicated.

Conversion to Monotherapy: Initiate Felbatol® at 1200 mg/day in divided doses three or four times daily. Reduce the dosage of concomitant AEDs by one-third at initiation of Felbatol® therapy. At week 2, increase the Felbatol® dosage to 2400 mg/day while reducing the dosage of other AEDs up to an additional one-third of their original dosage. At week 3, increase the Felbatol® dosage up to 3600 mg/day and continue to reduce the dosage of other AEDs as clinically indicated.

Adjunctive Therapy: Felbatol® should be added at 1200 mg/day in divided doses three or four times daily while reducing present AEDs by 20% in order to control plasma concentrations of concurrent phenytoin, valproic acid, and carbamazepine and its metabolites. Further reductions of the concomitant AEDs dosage may be necessary to minimize side effects due to drug interactions. Increase the dosage of Felbatol® by 1200 mg/day increments at weekly intervals to 3600 mg/day. Most side effects seen during Felbatol® adjunctive therapy resolve as the dosage of concomitant AEDs is decreased.

Dosage Table (adults)

	WEEK 1	WEEK 2	WEEK 3
Dosage reduction of concomitant AEDs	REDUCE original dose by 20–33%*	REDUCE original dose by up to an additional 1/3*	REDUCE as clinically indicated
Felbatol® Dosage	1200 mg/day Initial dose	2400 mg/day Therapeutic dosage range	3600 mg/day Therapeutic dosage range

*See ***Adjunctive*** and ***Conversion to Monotherapy*** sections.

While the above Felbatol® conversion guidelines may result in a Felbatol® 3600 mg/day dose within 3 weeks, in some patients titration to a 3600 mg/day Felbatol® dose has been achieved in as little as 3 days with appropriate adjustment of other AEDs.

Children with Lennox-Gastaut Syndrome (Ages 2–14 years)

Adjunctive Therapy: Felbatol® should be added at 15 mg/kg/day in divided doses three or four times daily while reducing present AEDs by 20% in order to control plasma levels of concurrent phenytoin, valproic acid, and carbamazepine and its metabolites. Further reductions of the concomitant AED

Continued on next page

Wallace Laboratories—Cont.

dosage may be necessary to minimize side effects due to drug interactions. Increase the dosage of Felbatol® by 15 mg/kg/day increments at weekly intervals to 45 mg/kg/day. Most side effects seen during Felbatol® adjunctive therapy resolve as the dosage of concomitant AEDs is decreased.

HOW SUPPLIED

Felbatol® (felbamate) Tablets, 400 mg, are yellow, scored, capsule-shaped tablets, debossed "0430" on one side and "WALLACE" on the other; available in:

Bottles of 100 ..... NDC 0037-0430-01
Unit Dose 100's ..... NDC 0037-0430-11

Felbatol® (felbamate) Tablets, 600 mg, are peach-colored, scored, capsule-shaped tablets, debossed "0431" on one side and "WALLACE" on the other; available in:

Bottles of 100 ..... NDC 0037-0431-01
Unit Dose 100's ..... NDC 0037-0431-11

Felbatol® (felbamate) Oral Suspension, 600 mg/5 mL, is peach-colored; available in:

8 oz bottles ..... NDC 0037-0442-67
32 oz bottles ..... NDC 0037-0442-17

Shake suspension well before using.
Store at controlled room temperature 15°–30°C (59°–86°F). Dispense in tight container.

PATIENT INFORMATION/CONSENT

FELBATOL® (felbamate) SHOULD NOT BE USED BY PATIENTS UNTIL THERE HAS BEEN A COMPLETE DISCUSSION OF THE RISKS AND WRITTEN INFORMED CONSENT HAS BEEN OBTAINED.

IMPORTANT INFORMATION AND WARNING:
Felbatol®, taken by itself or with other prescription and/or non-prescription drugs, can result in severe, potentially fatal blood abnormality ("aplastic anemia") and/or severe, potentially fatal liver damage.

PATIENT CONSENT:

My [My son, daughter, ward, _____ 's] treatment with Felbatol® has been personally explained to me by Dr. _____.
The following points of information, among others, have been specifically discussed and made clear and I have had the opportunity to ask any questions concerning this information.

1. I, _____ (Patient's Name), understand that Felbatol® is used to treat certain types of seizures and my physician has told me that I have this type(s) of seizures;
INITIALS: _____

2. I understand that Felbatol® is being used since my seizures have not been satisfactorily treated with other antiepileptic drugs;
INITIALS: _____

3. I understand there is a serious risk that I could develop aplastic anemia and/or liver failure, both of which are potentially fatal, by using Felbatol®;
INITIALS: _____

4. I understand that there are no laboratory tests which will predict if I am at an increased risk for one of the potentially fatal conditions;
INITIALS: _____

5. I understand that I should have the recommended blood work before my treatment with Felbatol® is begun or continued and then every 1–2 weeks while taking Felbatol®. I understand that although this blood work may help detect if I develop one of these conditions, it may do so only after significant, irreversible and potentially fatal damage has already occurred;
INITIALS: _____

6. If I am currently taking another antiepileptic drug, I understand that the manufacturer of Felbatol® recommends that the dosage of these other drugs be decreased by a certain amount when Felbatol® is started; if my physician determines that this should not be done in my case, he/she has explained the reason(s) for this decision;
INITIALS: _____

7. I understand that I must immediately report any unusual symptoms to Dr. _____ and be especially aware of any rashes, easy bruising, bleeding, sore throats, fever, and/or dark urine;
INITIALS: _____

I now authorize Dr. _____ to begin my treatment with Felbatol®; OR, if my treatment has already begun with Felbatol®, to continue such treatment.

_____
Patient, Parent, or Guardian

_____
Address

_____
Telephone

PHYSICIAN STATEMENT:

I have fully explained to the patient, _____, the nature and purpose of the treatment with Felbatol® (felbamate) and the potential risks associated with that treatment. I have asked the patient if he/she has any questions regarding this treatment or the risks and have answered those questions to the best of my ability. I also acknowledge that I have read and understand the prescribing information listed above.

_____ _____
Physician Date

NOTE TO PHYSICIAN: It is strongly recommended that you retain a signed copy of the informed consent with the patient's medical records.

SUPPLY OF PATIENT INFORMATION/CONSENT FORMS:
A supply of "Patient Information/Consent" forms as printed above is available, free of charge, from your local Wallace representative, or may be obtained by calling 609-655-6147. Permission to use the above Patient Information/Consent by photocopy reproduction is also hereby granted by Carter-Wallace, Inc.

CAUTION: Federal law prohibits dispensing without prescription.

WALLACE LABORATORIES
Division of Carter-Wallace, Inc.
Cranbury, New Jersey 08512
Rev. 10/94 IN-00431-06 PP

Shown in Product Identification Guide, page 338 & 339

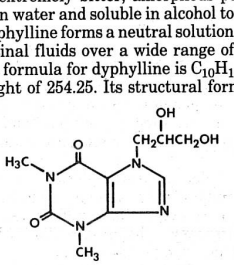
LUFYLLIN® ℞
(dyphylline)
Elixir

LUFYLLIN® Injection ℞
(dyphylline injection USP)
FOR INTRAMUSCULAR USE ONLY

LUFYLLIN® Tablets ℞
(dyphylline tablets, USP, 200 mg)
LUFYLLIN®–400 Tablets ℞
(dyphylline tablets, USP, 400 mg)

DESCRIPTION

LUFYLLIN (dyphylline), a xanthine derivative, is a bronchodilator available for oral administration as tablets containing 200 mg and 400 mg of dyphylline. Other ingredients: magnesium stearate, microcrystalline cellulose.
Chemically, dyphylline is 7-(2,3-dihydroxypropyl)-theophylline, a white, extremely bitter, amorphous powder that is freely soluble in water and soluble in alcohol to the extent of 2 g/100 ml. Dyphylline forms a neutral solution that is stable in gastrointestinal fluids over a wide range of pH.
The molecular formula for dyphylline is $C_{10}H_{14}N_4O_4$ with a molecular weight of 254.25. Its structural formula is:



CLINICAL PHARMACOLOGY

Dyphylline is a xanthine derivative with pharmacologic actions similar to theophylline and other members of this class of drugs. Its primary action is that of bronchodilation, but it also exhibits peripheral vasodilatory and other smooth muscle relaxant activity to a lesser degree. The bronchodilatory action of dyphylline, as with other xanthines, is thought to be mediated through competitive inhibition of phosphodiesterase with a resulting increase in cyclic AMP producing relaxation of bronchial smooth muscle.
LUFYLLIN is well tolerated and produces less nausea than aminophylline and other alkaline theophylline compounds when administered orally. Unlike the hydrolyzable salts of theophylline, dyphylline is not converted to free theophylline *in vivo*. It is absorbed rapidly in therapeutically active form and in healthy volunteers reaches a mean peak plasma concentration of 17.1 mcg/ml in approximately 45 minutes following a single oral dose of 1000 mg of LUFYLLIN.
Dyphylline exerts its bronchodilatory effects directly and, unlike theophylline, is excreted unchanged by the kidneys without being metabolized by the liver. Because of this, dyphylline pharmacokinetics and plasma levels are not influenced by various factors that affect liver function and hepatic enzyme activity, such as smoking, age, congestive heart failure or concomitant use of drugs which affect liver function.
The elimination half-life of dyphylline is approximately two hours (1.8–2.1 hr) and approximately 88% of a single oral dose can be recovered from the urine unchanged. The renal clearance would be correspondingly reduced in patients with impaired renal function. In anuric patients, the half-life may be increased 3 to 4 times normal.
Dyphylline plasma levels are dose-related and generally predictable. The range of plasma levels within which dyphylline can be expected to produce effective bronchodilation has not been determined.
Dyphylline plasma concentrations can be accurately determined using high pressure liquid chromatography (HPLC)* or gas-liquid chromatography (GLC).

See* Valia, *et al. J. Chromatogr.* **221: 170 (1980). Small quantities of pure dyphylline powder may be obtained from Wallace Laboratories, Cranbury, N.J. The internal standard, β-hydroxyethyltheophylline, may be obtained from companies supplying analytical chemicals.

INDICATIONS AND USAGE

For relief of acute bronchial asthma and for reversible bronchospasm associated with chronic bronchitits and emphysema.

CONTRAINDICATIONS

Hypersensitivity to dyphylline or related xanthine compounds.

WARNINGS

LUFYLLIN is not indicated in the management of status asthmaticus, which is a serious medical emergency.
Although the relationship between plasma levels of dyphylline and appearance of toxicity is unknown, excessive doses may be expected to be associated with an increased risk of adverse effects.

PRECAUTIONS

General: Use LUFYLLIN with caution in patients with severe cardiac disease, hypertension, hyperthyroidism, acute myocardial injury or peptic ulcer.
Drug interactions: Synergism between xanthine bronchodilators (e.g., theophylline), ephedrine and other sympathomimetic bronchodilators has been reported. This should be considered whenever these agents are prescribed concomitantly. Concurrent administration of dyphylline and probenecid, which competes for tubular secretion, has been shown to increase the plasma half-life of dyphylline (see Clinical Pharmacology).
Carcinogenesis, mutagenesis, impairment of fertility: No long-term animal studies have been performed with LUFYLLIN.
Pregnancy: Teratogenic effects—Pregnancy Category C. Animal reproduction studies have not been conducted with LUFYLLIN. It is also not known if LUFYLLIN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. LUFYLLIN should be given to a pregnant woman only if clearly needed.
Nursing mothers: Dyphylline is present in human milk at approximately twice the maternal plasma concentration. Caution should be exercised when LUFYLLIN is administered to a nursing woman.
Pediatric use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions with the use of LUFYLLIN have been infrequent, relatively mild, and rarely required reduction in dosage or withdrawal of therapy.
The following adverse reactions which have been reported with other xanthine bronchodilators, and which have most often been related to excessive drug plasma levels, should be considered as potential adverse effects when dyphylline is administered:
Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.