FELBATOL® (felbamate)
Tablets 400 mg and 600 mg, Oral Suspension 600 mg/5 mL
IN-00431-18 Rev. 7/11

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 BEEN PROVIDED THE FELBATOL WRITTEN ACKNOWLEDGEMENT (SEE PATIENT/PHYSICIAN ACKNOWLEDGMENT FORM).

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

EVALUATION OF POSTMARKETING EXPERIENCE SUGGESTS THAT ACUTE LIVER FAILURE IS ASSOCIATED WITH THE USE OF FELBATOL®. THE REPORTED RATE IN THE U.S. HAS BEEN ABOUT 6 CASES OF LIVER FAILURE LEADING TO DEATH OR TRANSPLANT PER 75,000 PATIENT YEARS OF USE. THIS RATE IS AN UNDERESTIMATE BECAUSE OF UNDER REPORTING, AND THE TRUE RATE COULD BE CONSIDERABLY GREATER THAN THIS. FOR EXAMPLE, IF THE REPORTING RATE IS 10%, THE TRUE RATE WOULD BE ONE CASE PER 1,250 PATIENT YEARS OF USE.

OF THE CASES REPORTED, ABOUT 67% RESULTED IN DEATH OR LIVER TRANSPLANTATION, USUALLY WITHIN 5 WEEKS OF THE ONSET OF SIGNS AND SYMPTOMS OF LIVER FAILURE. THE EARLIEST ONSET OF SEVERE HEPATIC DYSFUNCTION FOLLOWED SUBSEQUENTLY BY LIVER FAILURE WAS 3 WEEKS AFTER INITIATION OF FELBATOL®. ALTHOUGH SOME REPORTS DESCRIBED DARK URINE AND NONSPECIFIC PRODROMAL SYMPTOMS (E.G., ANOREXIA, MALAISE, AND GASTROINTESTINAL SYMPTOMS), IN OTHER REPORTS IT WAS NOT CLEAR IF ANY PRODROMAL SYMPTOMS PRECEDED THE ONSET OF JAUNDICE.

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 AFFECT THE INCIDENCE OF HEPATIC FAILURE.

FELBATOL® SHOULD NOT BE PRESCRIBED FOR ANYONE WITH A HISTORY OF HEPATIC DYSFUNCTION.

TREATMENT WITH FELBATOL® SHOULD BE INITIATED ONLY IN INDIVIDUALS WITHOUT ACTIVE LIVER DISEASE AND WITH NORMAL BASELINE SERUM TRANSAMINASES. IT HAS NOT BEEN PROVED THAT PERIODIC SERUM TRANSAMINASE TESTING WILL PREVENT SERIOUS INJURY BUT IT IS GENERALLY BELIEVED THAT EARLY DETECTION OF DRUG-INDUCED HEPATIC INJURY ALONG WITH IMMEDIATE WITHDRAWAL OF THE SUSPECT DRUG ENHANCES THE LIKELIHOOD FOR RECOVERY. THERE IS NO INFORMATION AVAILABLE THAT DOCUMENTS HOW RAPIDLY PATIENTS CAN PROGRESS FROM

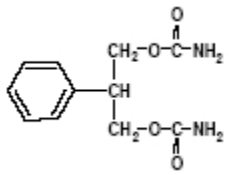
NORMAL LIVER FUNCTION TO LIVER FAILURE, BUT OTHER DRUGS KNOWN TO BE HEPATOTOXINS CAN CAUSE LIVER FAILURE RAPIDLY (E.G., FROM NORMAL ENZYMES TO LIVER FAILURE IN 2-4 WEEKS). ACCORDINGLY, MONITORING OF SERUM TRANSAMINASE LEVELS (AST AND ALT) IS RECOMMENDED AT BASELINE AND PERIODICALLY THEREAFTER. WHILE THE MORE FREQUENT THE MONITORING THE GREATER THE CHANCES OF EARLY DETECTION, THE PRECISE SCHEDULE FOR MONITORING IS A MATTER OF CLINICAL JUDGEMENT.

FELBATOL® SHOULD BE DISCONTINUED IF EITHER SERUM AST OR SERUM ALT LEVELS BECOME INCREASED ≥ 2 TIMES THE UPPER LIMIT OF NORMAL, OR IF CLINICAL SIGNS AND SYMPTOMS SUGGEST LIVER FAILURE (SEE PRECAUTIONS). PATIENTS WHO DEVELOP EVIDENCE OF HEPATOCELLULAR INJURY WHILE ON FELBATOL® AND ARE WITHDRAWN FROM THE DRUG FOR ANY REASON SHOULD BE PRESUMED TO BE AT INCREASED RISK FOR LIVER INJURY IF FELBATOL® IS REINTRODUCED. ACCORDINGLY, SUCH PATIENTS SHOULD NOT BE CONSIDERED FOR RE-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) Oral 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). Linear and dose proportional pharmacokinetics were also observed at doses above 3600 mg/day up to the maximum dose studied of 6000 mg/day. 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 hepatic functional impairment have not been evaluated.

Renal Impairment:
Felbamate's single dose monotherapy pharmacokinetic parameters were evaluated in 12 otherwise healthy individuals with renal impairment. There was a 40-50% reduction in total body clearance and 9-15 hours prolongation of half-life in renally impaired subjects compared to that in subjects with normal renal

function. Reduced felbamate clearance and a longer half-life were associated with diminishing renal function.

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

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