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

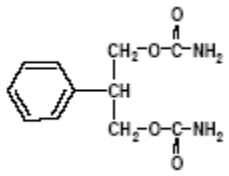
NORMAL LIVER FUNCTION TO LIVER FAILURE, BUT OTHER DRUGS KNOWN TO BE HEPATOTOXINS CAN CAUSE LIVER FAILURE RAPIDLY (E.G., FROM NORMAL ENZYMES TO LIVER FAILURE IN 2-4 WEEKS). ACCORDINGLY, MONITORING OF SERUM TRANSAMINASE LEVELS (AST AND ALT) IS RECOMMENDED AT BASELINE AND PERIODICALLY THEREAFTER. WHILE 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

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 acknowledgement, 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.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs) including Felbatol ®, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Felbatol or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

PRECAUTIONS

Dosage Adjustment in the Renally Impaired: A study in otherwise healthy individuals with renal dysfunction indicated that prolonged half-life and reduced clearance of felbamate are associated with diminishing renal function. Felbamate should be used with caution in patients with renal dysfunction (see **DOSAGE AND ADMINISTRATION**).

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 acknowledgement prior to initiation of Felbatol® therapy (see **PATIENT/PHYSICIAN ACKNOWLEDGMENT FORM** section).

Patients should be instructed to read the Medication Guide supplied as required by law when Felbatol® is dispensed. The complete text of the Medication Guide is reprinted at the end of this document.

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®.

Patients should be advised to be alert for signs of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they should occur.

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.

See Box Warnings for recommended monitoring of serum transaminases. If significant, confirmed liver abnormalities are detected during the course of Felbatol® treatment, Felbatol® should be discontinued immediately with continued liver function monitoring until values return to normal. (see **PATIENT/PHYSICIAN ACKNOWLEDGMENT FORM**).

Suicidal Thinking and Behavior: Patients, their caregivers, and families should be counseled that AEDs, including Felbatol®, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Pregnancy: Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see **Pregnancy** section).

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 Table 2:

Table 2 Steady-State Plasma Concentrations of Felbatol When Coadministered With Other AEDs

AED Coadministered	AED Concentration	Felbatol® Concentration
Phenytoin	↑	↓
Valproate	↑	↔**

Carbamazepine (CBZ) *CBZ epoxide	↓ ↑	↓
Phenobarbital	↑	↓
*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®.

Phenobarbital: Coadministration of felbamate with phenobarbital causes an increase in phenobarbital plasma concentrations. In 12 otherwise healthy male volunteers ingesting phenobarbital, the steady-state trough (Cmin) phenobarbital concentration was 14.2 micrograms/mL. The steady-state Cmin concentration increased to 17.8 micrograms/mL when 2400 mg/day of felbamate was coadministered for one week.

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.

Phenobarbital: It appears that phenobarbital may reduce plasma felbamate concentrations. Steady-state plasma felbamate concentrations were found to be 29% lower than the mean concentrations of a group of newly diagnosed subjects with epilepsy also receiving 2400 mg of felbamate a day.

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.

Effects of Erythromycin on Felbatol®:
The coadministration of erythromycin (1000 mg/day) for 10 days did not alter the pharmacokinetic parameters of Cmax, Cmin, AUC, Cl/kg or Tmax at felbamate daily doses of 3000 or 3600 mg/day in 10 otherwise healthy subjects with epilepsy.

Effects of Felbatol® on Low-Dose Combination Oral Contraceptives:
A group of 24 nonsmoking, healthy white female volunteers established on an oral contraceptive regimen containing 30 µg ethinyl estradiol and 75 µg gestodene for at least 3 months received 2400 mg/day of felbamate from midcycle (day 15) to midcycle (day 14) of two consecutive oral contraceptive cycles. Felbamate treatment resulted in a 42% decrease in the gestodene AUC 0-24, but no clinically relevant effect was observed on the pharmacokinetic parameters of ethinyl estradiol. No volunteer showed hormonal evidence of ovulation, but one volunteer reported intermenstrual bleeding during felbamate treatment.

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 nongenotoxic 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.

To provide information regarding the effects of in utero exposure to Felbatol®, physicians are advised to recommend that pregnant patients taking Felbatol enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

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

To report SUSPECTED ADVERSE REACTIONS, contact Meda Pharmaceuticals Inc. at 1-800-526-3840 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch* .

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. Table 3 presents reported adverse events that were classified using standard WHO-based dictionary terminology.

Table 3 Adults Treatment-Emergent Adverse Event Incidence in Controlled Monotherapy Trials

	Felbatol®* (N=58)	Low Dose Valproate** (N=50)
Body System Event	%	%
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:
Table 4 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.

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Table 4 Adults Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials		
	Felbatol®	Placebo
	(N=114)	(N=43)
Body System/Event	%	%
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

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Children

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

Table 5 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.

Table 5 Children Treatment-Emergent Adverse Event Incidence in Controlled Add-On Lennox-Gastaut Trials

	Felbatol®	Placebo
	(N=31)	(N=27)
Body System/Event	%	%
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, L.E. syndrome, SIDS, sudden death, edema, hypothermia, rigors, hyperpyrexia.
Cardiovascular: atrial fibrillation, atrial arrhythmia, cardiac arrest, torsade de pointes, cardiac failure, hypotension, hypertension, flushing, thrombophlebitis, ischemic necrosis, gangrene, peripheral ischemia, bradycardia, Henoch-Schönlein purpura (vasculitis).
Central & Peripheral Nervous System: delusion, paralysis, mononeuritis, cerebrovascular disorder, cerebral edema, coma, manic reaction, encephalopathy, paranoid reaction, nystagmus, choreoathetosis, extrapyramidal disorder, confusion, psychosis, status epilepticus, dyskinesia, dysarthria, respiratory depression, apathy, concentration impaired.
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, rectal hemorrhage, flatulence, gingival bleeding, acquired megacolon, ileus, intestinal obstruction, enteritis, ulcerative stomatitis, glossitis, dysphagia, jaundice, gastric ulcer, gastric dilatation, gastroesophageal reflux.
Fetal Disorders: fetal death, microcephaly, genital malformation, anencephaly, encephalocele.
Hematologic: (Refer to **WARNINGS**) increased and decreased prothrombin time, anemia, hypochromic anemia, aplastic anemia, pancytopenia, hemolytic uremic syndrome, increased mean corpuscular volume

(mcv) with and without anemia, coagulation disorder, embolism-limb, disseminated intravascular coagulation, eosinophilia, hemolytic anemia, leukemia, including myelogenous leukemia, and lymphoma, including T-cell and B-cell lymphoproliferative disorders.
Metabolic/Nutritional: hypernatremia, hypoglycemia, SIADH, hypomagnesemia, dehydration, hyperglycemia, hypocalcemia.
Musculoskeletal: arthralgia, muscle weakness, involuntary muscle contraction, rhabdomyolysis.
Respiratory: dyspnea, pneumonia, pneumonitis, hypoxia, epistaxis, pleural effusion, respiratory insufficiency, pulmonary hemorrhage, asthma.
Special Senses: hemianopsia, decreased hearing, conjunctivitis.
Urogenital: menstrual disorder, acute renal failure, hepatorenal syndrome, hematuria, urinary retention, nephrosis, vaginal hemorrhage, abnormal renal function, dysuria, placental disorder.

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).

Dosage Adjustment in the Renally Impaired: Felbamate should be used with caution in patients with renal dysfunction. In the renally impaired, starting and maintenance doses should be reduced by one-half (see **CLINICAL PHARMACOLOGY** / **Pharmacokinetics** and **PRECAUTIONS**). Adjunctive therapy with medications which affect felbamate plasma concentrations, especially AEDs, may warrant further reductions in felbamate daily doses in patients with renal dysfunction.

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, phenobarbital, 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.

Table 6 Dosage Table (adults)

	WEEK 1 REDUCE original dose by 20–33%*	**WEEK 2** REDUCE original dose by up to an additional 1/3*	**WEEK 3** REDUCE as clinically indicated
Dosage reduction of concomitant AEDs			
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, phenobarbital, 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 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 FELBATOL 400 on the other; available in bottles of 100 (NDC 0037-0430-01). Felbatol® (felbamate) Tablets, 600 mg, are peach-colored, scored, capsule-shaped tablets, debossed 0431 on one side and FELBATOL 600 on the other; available in bottles of 100 (NDC 0037-0431-01). Felbatol® (felbamate) Oral Suspension, 600 mg/5 mL, is peach-colored; available in 8 oz bottles (NDC 0037-0442-67) and 32 oz bottles (NDC 0037-0442-17).

Shake suspension well before using. Store at controlled room temperature 20°-25°C (68°-77°F). Dispense in tight container.

To report SUSPECTED ADVERSE REACTIONS, contact Meda Pharmaceuticals Inc. at 1-800-526-3840 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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Somerset, NJ 08873
IN-00431-18 Rev. 7/11

PATIENT/PHYSICIAN ACKNOWLEDGMENT FORM

FELBATOL® (felbamate) SHOULD NOT BE USED BY PATIENTS UNTIL THERE HAS BEEN A COMPLETE DISCUSSION OF THE RISKS.
All patients treated with Felbatol should acknowledge that they understand the risks and other information about Felbatol discussed below, and physicians should acknowledge this discussion.

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

PATIENT ACKNOWLEDGMENT:

Do not sign this form if there is anything you do not understand about the information you have received. Ask your doctor about anything you do not understand before you initial any of the items below or sign this form.

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 because my seizures have not been satisfactorily treated with other antiepileptic drugs;
INITIALS: _____

3. I understand that 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 (baseline) and periodically thereafter as clinical judgement warrants. 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 other antiepileptic drugs, 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: _____

8. I understand that antiepileptic drugs such as Felbatol® may increase the risk of suicidal thoughts and behavior. I understand that I must immediately report any unusual changes in mood or behavior, symptoms of depression or thoughts about self-harm to Dr. _____.
INITIALS: _____

_____
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.

_____
Physician Date

Revised: 7/11

NOTE TO PHYSICIAN: It is strongly recommended that you retain a signed copy of the Patient/Physician Acknowledgment Form with the patient's medical records.

SUPPLY OF PATIENT/PHYSICIAN ACKNOWLEDGMENT FORMS:
A supply of "Patient/Physician Acknowledgement" Forms as printed above is available, free of charge, from your local MEDA Pharmaceuticals representative, or may be obtained by calling 1-800-526-3840. Permission to use the above Patient/Physician Acknowledgment Form by photocopy reproduction is also hereby granted by MEDA Pharmaceuticals Inc.

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