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1 FELBATOL® (felbamate)  
2 Tablets 400 mg and 600 mg, Oral Suspension 600 mg/5 mL  
3 IN-00431-18 Rev. 7/11  
4

5 **Before Prescribing Felbatol® (felbamate), the physician should be thoroughly familiar with the**  
6 **details of this prescribing information.**  
7

8 **FELBATOL® SHOULD NOT BE USED BY PATIENTS UNTIL THERE HAS BEEN A**  
9 **COMPLETE DISCUSSION OF THE RISKS AND THE PATIENT, PARENT, OR GUARDIAN**  
10 **HAS BEEN PROVIDED THE FELBATOL WRITTEN ACKNOWLEDGEMENT (SEE**  
11 **PATIENT/PHYSICIAN ACKNOWLEDGMENT FORM).**  
12

13 **WARNING**

14 **1. APLASTIC ANEMIA**

15 THE USE OF FELBATOL® (felbamate) IS ASSOCIATED WITH A MARKED INCREASE IN THE  
16 INCIDENCE OF APLASTIC ANEMIA. ACCORDINGLY, FELBATOL® SHOULD ONLY BE USED  
17 IN PATIENTS WHOSE EPILEPSY IS SO SEVERE THAT THE RISK OF APLASTIC ANEMIA IS  
18 DEEMED ACCEPTABLE IN LIGHT OF THE BENEFITS CONFERRED BY ITS USE (SEE  
19 **INDICATIONS**). ORDINARILY, A PATIENT SHOULD NOT BE PLACED ON AND/OR  
20 CONTINUED ON FELBATOL® WITHOUT CONSIDERATION OF APPROPRIATE EXPERT  
21 HEMATOLOGIC CONSULTATION.  
22

23 AMONG FELBATOL® TREATED PATIENTS, APLASTIC ANEMIA (PANCYTOPENIA IN THE  
24 PRESENCE OF A BONE MARROW LARGELY DEPLETED OF HEMATOPOIETIC PRECURSORS)  
25 OCCURS AT AN INCIDENCE THAT MAY BE MORE THAN A 100 FOLD GREATER THAN THAT  
26 SEEN IN THE UNTREATED POPULATION (I.E., 2 TO 5 PER MILLION PERSONS PER YEAR).  
27 THE RISK OF DEATH IN PATIENTS WITH APLASTIC ANEMIA GENERALLY VARIES AS A  
28 FUNCTION OF ITS SEVERITY AND ETIOLOGY; CURRENT ESTIMATES OF THE OVERALL  
29 CASE FATALITY RATE ARE IN THE RANGE OF 20 TO 30%, BUT RATES AS HIGH AS 70%  
30 HAVE BEEN REPORTED IN THE PAST.  
31

32 THERE ARE TOO FEW FELBATOL® ASSOCIATED CASES, AND TOO LITTLE KNOWN ABOUT  
33 THEM TO PROVIDE A RELIABLE ESTIMATE OF THE SYNDROME'S INCIDENCE OR ITS CASE  
34 FATALITY RATE OR TO IDENTIFY THE FACTORS, IF ANY, THAT MIGHT CONCEIVABLY BE  
35 USED TO PREDICT WHO IS AT GREATER OR LESSER RISK.  
36

37 IN MANAGING PATIENTS ON FELBATOL®, IT SHOULD BE BORNE IN MIND THAT THE  
38 CLINICAL MANIFESTATION OF APLASTIC ANEMIA MAY NOT BE SEEN UNTIL AFTER A  
39 PATIENT HAS BEEN ON FELBATOL® FOR SEVERAL MONTHS (E.G., ONSET OF APLASTIC  
40 ANEMIA AMONG FELBATOL® EXPOSED PATIENTS FOR WHOM DATA ARE AVAILABLE  
41 HAS RANGED FROM 5 TO 30 WEEKS). HOWEVER, THE INJURY TO BONE MARROW STEM  
42 CELLS THAT IS HELD TO BE ULTIMATELY RESPONSIBLE FOR THE ANEMIA MAY OCCUR  
43 WEEKS TO MONTHS EARLIER. ACCORDINGLY, PATIENTS WHO ARE DISCONTINUED  
44 FROM FELBATOL® REMAIN AT RISK FOR DEVELOPING ANEMIA FOR A VARIABLE, AND  
45 UNKNOWN, PERIOD AFTERWARDS.  
46

47 IT IS NOT KNOWN WHETHER OR NOT THE RISK OF DEVELOPING APLASTIC ANEMIA  
48 CHANGES WITH DURATION OF EXPOSURE. CONSEQUENTLY, IT IS NOT SAFE TO ASSUME  
49 THAT A PATIENT WHO HAS BEEN ON FELBATOL® WITHOUT SIGNS OF HEMATOLOGIC  
50 ABNORMALITY FOR LONG PERIODS OF TIME IS WITHOUT RISK.

51 IT IS NOT KNOWN WHETHER OR NOT THE DOSE OF FELBATOL® AFFECTS THE  
52 INCIDENCE OF APLASTIC ANEMIA.

53  
54 IT IS NOT KNOWN WHETHER OR NOT CONCOMITANT USE OF ANTIEPILEPTIC DRUGS  
55 AND/OR OTHER DRUGS AFFECTS THE INCIDENCE OF APLASTIC ANEMIA.

56  
57 APLASTIC ANEMIA TYPICALLY DEVELOPS WITHOUT PREMONITORY CLINICAL OR  
58 LABORATORY SIGNS, THE FULL BLOWN SYNDROME PRESENTING WITH SIGNS OF  
59 INFECTION, BLEEDING, OR ANEMIA. ACCORDINGLY, ROUTINE BLOOD TESTING CANNOT  
60 BE RELIABLY USED TO REDUCE THE INCIDENCE OF APLASTIC ANEMIA, BUT, IT WILL, IN  
61 SOME CASES, ALLOW THE DETECTION OF THE HEMATOLOGIC CHANGES BEFORE THE  
62 SYNDROME DECLARES ITSELF CLINICALLY. FELBATOL® SHOULD BE DISCONTINUED IF  
63 ANY EVIDENCE OF BONE MARROW DEPRESSION OCCURS.

64  
65 **2. HEPATIC FAILURE**

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

73  
74 OF THE CASES REPORTED, ABOUT 67% RESULTED IN DEATH OR LIVER  
75 TRANSPLANTATION, USUALLY WITHIN 5 WEEKS OF THE ONSET OF SIGNS AND  
76 SYMPTOMS OF LIVER FAILURE. THE EARLIEST ONSET OF SEVERE HEPATIC  
77 DYSFUNCTION FOLLOWED SUBSEQUENTLY BY LIVER FAILURE WAS 3 WEEKS AFTER  
78 INITIATION OF FELBATOL®. ALTHOUGH SOME REPORTS DESCRIBED DARK URINE AND  
79 NONSPECIFIC PRODROMAL SYMPTOMS (E.G., ANOREXIA, MALAISE, AND  
80 GASTROINTESTINAL SYMPTOMS), IN OTHER REPORTS IT WAS NOT CLEAR IF ANY  
81 PRODROMAL SYMPTOMS PRECEDED THE ONSET OF JAUNDICE.

82  
83 IT IS NOT KNOWN WHETHER OR NOT THE RISK OF DEVELOPING HEPATIC FAILURE  
84 CHANGES WITH DURATION OF EXPOSURE.

85  
86 IT IS NOT KNOWN WHETHER OR NOT THE DOSAGE OF FELBATOL® AFFECTS THE  
87 INCIDENCE OF HEPATIC FAILURE.

88  
89 IT IS NOT KNOWN WHETHER CONCOMITANT USE OF OTHER ANTIEPILEPTIC DRUGS  
90 AND/OR OTHER DRUGS AFFECT THE INCIDENCE OF HEPATIC FAILURE.

91  
92 FELBATOL® SHOULD NOT BE PRESCRIBED FOR ANYONE WITH A HISTORY OF HEPATIC  
93 DYSFUNCTION.

94  
95 TREATMENT WITH FELBATOL® SHOULD BE INITIATED ONLY IN INDIVIDUALS WITHOUT  
96 ACTIVE LIVER DISEASE AND WITH NORMAL BASELINE SERUM TRANSAMINASES. IT HAS  
97 NOT BEEN PROVED THAT PERIODIC SERUM TRANSAMINASE TESTING WILL PREVENT  
98 SERIOUS INJURY BUT IT IS GENERALLY BELIEVED THAT EARLY DETECTION OF DRUG-  
99 INDUCED HEPATIC INJURY ALONG WITH IMMEDIATE WITHDRAWAL OF THE SUSPECT  
100 DRUG ENHANCES THE LIKELIHOOD FOR RECOVERY. THERE IS NO INFORMATION  
101 AVAILABLE THAT DOCUMENTS HOW RAPIDLY PATIENTS CAN PROGRESS FROM

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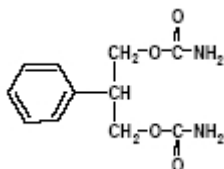
102 NORMAL LIVER FUNCTION TO LIVER FAILURE, BUT OTHER DRUGS KNOWN TO BE  
103 HEPATOTOXINS CAN CAUSE LIVER FAILURE RAPIDLY (E.G., FROM NORMAL ENZYMES  
104 TO LIVER FAILURE IN 2-4 WEEKS). ACCORDINGLY, MONITORING OF SERUM  
105 TRANSAMINASE LEVELS (AST AND ALT) IS RECOMMENDED AT BASELINE AND  
106 PERIODICALLY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

109  
110 FELBATOL® SHOULD BE DISCONTINUED IF EITHER SERUM AST OR SERUM ALT LEVELS  
111 BECOME INCREASED  $\geq 2$  TIMES THE UPPER LIMIT OF NORMAL, OR IF CLINICAL SIGNS  
112 AND SYMPTOMS SUGGEST LIVER FAILURE (SEE PRECAUTIONS ). PATIENTS WHO  
113 DEVELOP EVIDENCE OF HEPATOCELLULAR INJURY WHILE ON FELBATOL® AND ARE  
114 WITHDRAWN FROM THE DRUG FOR ANY REASON SHOULD BE PRESUMED TO BE AT  
115 INCREASED RISK FOR LIVER INJURY IF FELBATOL® IS REINTRODUCED. ACCORDINGLY,  
116 SUCH PATIENTS SHOULD NOT BE CONSIDERED FOR RE-TREATMENT.

## 117 118 DESCRIPTION

119 Felbatol® (felbamate) is an antiepileptic available as 400 mg and 600 mg tablets and as a 600 mg/5 mL  
120 suspension for oral administration. Its chemical name is 2-phenyl-1,3-propanediol dicarbamate.

121  
122 Felbamate is a white to off-white crystalline powder with a characteristic odor. It is very slightly soluble  
123 in water, slightly soluble in ethanol, sparingly soluble in methanol, and freely soluble in dimethyl  
124 sulfoxide. The molecular weight is 238.24; felbamate's molecular formula is  $C_{11}H_{14}N_2O_4$ ; its  
125 structural formula is:  
126



127  
128  
129 The inactive ingredients for Felbatol® (felbamate) Tablets 400 mg and 600 mg are starch,  
130 microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, FD&C Yellow No. 6,  
131 D&C Yellow No. 10, and FD&C Red No. 40 (600 mg tablets only). The inactive ingredients for  
132 Felbatol® (felbamate) Oral Suspension 600 mg/5 mL are sorbitol, glycerin, microcrystalline cellulose,  
133 carboxymethylcellulose sodium, simethicone, polysorbate 80, methylparaben, saccharin sodium,  
134 propylparaben, FD&C Yellow No. 6, FD&C Red No. 40, flavorings, and purified water.

## 135 136 CLINICAL PHARMACOLOGY

### 137 Mechanism of Action:

138 The mechanism by which felbamate exerts its anticonvulsant activity is unknown, but in animal test  
139 systems designed to detect anticonvulsant activity, felbamate has properties in common with other  
140 marketed anticonvulsants. Felbamate is effective in mice and rats in the maximal electroshock test, the  
141 subcutaneous pentylenetetrazol seizure test, and the subcutaneous picrotoxin seizure test. Felbamate also  
142 exhibits anticonvulsant activity against seizures induced by intracerebroventricular administration of  
143 glutamate in rats and N-methyl-D,L-aspartic acid in mice. Protection against maximal electroshock-  
144 induced seizures suggests that felbamate may reduce seizure spread, an effect possibly predictive of  
145 efficacy in generalized tonic-clonic or partial seizures. Protection against pentylenetetrazol-induced  
146 seizures suggests that felbamate may increase seizure threshold, an effect considered to be predictive of  
147 potential efficacy in absence seizures.

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148

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

155

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

160

#### 161 **Pharmacokinetics:**

162 The numbers in the pharmacokinetic section are mean  $\pm$  standard deviation.

163

164 Felbamate is well-absorbed after oral administration. Over 90% of the radioactivity after a dose of  
165 1000 mg <sup>14</sup>C felbamate was found in the urine. Absolute bioavailability (oral vs. parenteral) has not been  
166 measured. The tablet and suspension were each shown to be bioequivalent to the capsule used in clinical  
167 trials, and pharmacokinetic parameters of the tablet and suspension are similar. There was no effect of  
168 food on absorption of the tablet; the effect of food on absorption of the suspension has not been evaluated.

169

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

174

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

178

179 Felbamate is excreted with a terminal half-life of 20-23 hours, which is unaltered after multiple doses.  
180 Clearance after a single 1200 mg dose is 26 $\pm$ 3 mL/hr/kg, and after multiple daily doses of 3600 mg is  
181 30 $\pm$ 8 mL/hr/kg. The apparent volume of distribution was 756 $\pm$ 82 mL/kg after a 1200 mg dose. Felbamate  
182 C<sub>max</sub> and AUC are proportionate to dose after single and multiple doses over a range of 100-800 mg  
183 single doses and 1200-3600 mg daily doses. C<sub>min</sub> (trough) blood levels are also dose proportional.  
184 Multiple daily doses of 1200, 2400, and 3600 mg gave C<sub>min</sub> values of 30 $\pm$ 5, 55 $\pm$ 8, and 83 $\pm$ 21  
185 micrograms/mL (N=10 patients). Linear and dose proportional pharmacokinetics were also observed at  
186 doses above 3600 mg/day up to the maximum dose studied of 6000 mg/day. Felbamate gave dose  
187 proportional steady-state peak plasma concentrations in children age 4-12 over a range of 15, 30, and 45  
188 mg/kg/day with peak concentrations of 17, 32, and 49 micrograms/mL.

189

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

193

#### 194 **Renal Impairment:**

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

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

200  
201 **Pharmacodynamics:**

202 *Typical Physiologic Responses:*

203 1. *Cardiovascular:*

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

208  
209 2. *Other Physiologic Effects:*

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

216  
217 **CLINICAL STUDIES**

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

221  
222 **Felbatol® Monotherapy Trials in Adults**

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

237  
238 In the multicenter trial, the percentage of patients who met escape criteria was 40% (18/45) in the  
239 Felbatol® group and 78% (39/50) in the low-dose valproate group. In the single-center trial, the  
240 percentage of patients who met escape criteria was 14% (3/21) in the Felbatol® group and 90% (19/21) in  
241 the low-dose valproate group. In both trials, the difference in the percentage of patients meeting escape  
242 criteria was statistically significant ( $P < .001$ ) in favor of Felbatol®. These two studies by design were  
243 intended to demonstrate the effectiveness of Felbatol® monotherapy. The studies were not designed or  
244 intended to demonstrate comparative efficacy of the two drugs. For example, valproate was not used at  
245 the maximally effective dose.

246  
247 **Felbatol® Adjunctive Therapy Trials in Adults**

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248 A double-blind, placebo-controlled crossover trial consisted of two 10-week outpatient treatment periods.  
249 Patients with refractory partial-onset seizures who were receiving phenytoin and carbamazepine at  
250 therapeutic levels were administered Felbatol® (felbamate) as add-on therapy at a starting dosage of 1400  
251 mg/day in three divided doses, which was increased to 2600 mg/day in three divided doses. Among the 56  
252 patients who completed the study, the baseline seizure frequency was 20 per month. Patients treated with  
253 Felbatol® had fewer seizures than patients treated with placebo for each treatment sequence. There was a  
254 23% (P=.018) difference in percentage seizure frequency reduction in favor of Felbatol®.  
255

256 Felbatol® 3600 mg/day given QID and placebo were compared in a 28-day double-blind add-on trial in  
257 patients who had their standard antiepileptic drugs reduced while undergoing evaluations for surgery of  
258 intractable epilepsy. All patients had confirmed partial-onset seizures with or without generalization,  
259 seizure frequency during surgical evaluation not exceeding an average of four partial seizures per day or  
260 more than one generalized seizure per day, and a minimum average of one partial or generalized tonic-  
261 clonic seizure per day for the last 3 days of the surgical evaluation. The primary efficacy variable was  
262 time to fourth seizure after randomization to treatment with Felbatol® or placebo. Thirteen (46%) of 28  
263 patients in the Felbatol® group versus 29 (88%) of 33 patients in the placebo group experienced a fourth  
264 seizure. The median times to fourth seizure were greater than 28 days in the Felbatol® group and 5 days  
265 in the placebo group. The difference between Felbatol® and placebo in time to fourth seizure was  
266 statistically significant (P=.002) in favor of Felbatol®.  
267

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

269 In a 70-day double-blind, placebo-controlled add-on trial in the Lennox-Gastaut syndrome, Felbatol® 45  
270 mg/kg/day given QID was superior to placebo in controlling the multiple seizure types associated with  
271 this condition. Patients had at least 90 atonic and/or atypical absence seizures per month while receiving  
272 therapeutic dosages of one or two other antiepileptic drugs. Patients had a past history of using an average  
273 of eight antiepileptic drugs. The most commonly used antiepileptic drug during the baseline period was  
274 valproic acid. The frequency of all types of seizures during the baseline period was 1617 per month in the  
275 Felbatol® group and 716 per month in the placebo group. Statistically significant differences in the effect  
276 on seizure frequency favored Felbatol® over placebo for total seizures (26% reduction vs. 5% increase,  
277 P<.001), atonic seizures (44% reduction vs. 7% reduction, P=.002), and generalized tonic-clonic seizures  
278 (40% reduction vs. 12% increase, P=.017). Parent/guardian global evaluations based on impressions of  
279 quality of life with respect to alertness, verbal responsiveness, general well-being, and seizure control  
280 significantly (P<.001) favored Felbatol® over placebo.  
281

282 When efficacy was analyzed by gender in four well-controlled trials of felbamate as adjunctive and  
283 monotherapy for partial-onset seizures and Lennox-Gastaut syndrome, a similar response was seen in 122  
284 males and 142 females.  
285

#### 286 **INDICATIONS AND USAGE**

287  
288 Felbatol® is not indicated as a first line antiepileptic treatment (see **Warnings**). Felbatol® is  
289 recommended for use only in those patients who respond inadequately to alternative treatments and  
290 whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed  
291 acceptable in light of the benefits conferred by its use.  
292

293 If these criteria are met and the patient has been fully advised of the risk, and has provided written  
294 acknowledgement, Felbatol® can be considered for either monotherapy or adjunctive therapy in the  
295 treatment of partial seizures, with and without generalization, in adults with epilepsy and as adjunctive  
296 therapy in the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in  
297 children.  
298

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299 **CONTRAINDICATIONS**

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

303  
304 **WARNINGS**

305 See Boxed Warning regarding aplastic anemia and hepatic failure.  
306 Antiepileptic drugs should not be suddenly discontinued because of the possibility of increasing seizure  
307 frequency.

308  
309 **Suicidal Behavior and Ideation**

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

314  
315 Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different  
316 AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted  
317 Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to  
318 placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate  
319 of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24%  
320 among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal  
321 thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in  
322 the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about  
323 drug effect on suicide.

324  
325 The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after  
326 starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most  
327 trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior  
328 beyond 24 weeks could not be assessed.

329  
330 The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The  
331 finding of increased risk with AEDs of varying mechanisms of action and across a range of indications  
332 suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by  
333 age (5-100 years) in the clinical trials analyzed.

334  
335 Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

<b>Table 1 Risk by Indication for Antiepileptic Drugs in the Pooled Analysis</b>				
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

336  
337 The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical  
338 trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and  
339 psychiatric indications.

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340

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

347

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

353

### 354 **PRECAUTIONS**

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

359

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

362

363 The physician should obtain written acknowledgement prior to initiation of Felbatol® therapy (see  
364 **PATIENT/PHYSICIAN ACKNOWLEDGMENT FORM** section).

365

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

369

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

373

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

378

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

382

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

386

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

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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:

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

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Carbamazepine (CBZ) *CBZ epoxide	↓ ↑	↓
Phenobarbital	↑	↓
*Not administered but an active metabolite of carbamazepine. **No significant effect.		

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***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.

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

484  
485 **Valproate:** Available data suggest that there is no significant effect of valproate on the clearance of  
486 Felbatol® at steady-state. Therefore, the addition of valproate is not expected to cause a clinically  
487 important effect on Felbatol® (felbamate) plasma concentrations.

488  
489 **Phenobarbital:** It appears that phenobarbital may reduce plasma felbamate concentrations. Steady-state  
490 plasma felbamate concentrations were found to be 29% lower than the mean concentrations of a group of  
491 newly diagnosed subjects with epilepsy also receiving 2400 mg of felbamate a day.

492  
493 **Effects of Antacids on Felbatol®:**  
494 The rate and extent of absorption of a 2400 mg dose of Felbatol® as monotherapy given as tablets was  
495 not affected when coadministered with antacids.

496  
497 **Effects of Erythromycin on Felbatol®:**  
498 The coadministration of erythromycin (1000 mg/day) for 10 days did not alter the pharmacokinetic  
499 parameters of C<sub>max</sub>, C<sub>min</sub>, AUC, Cl/kg or T<sub>max</sub> at felbamate daily doses of 3000 or 3600 mg/day in 10  
500 otherwise healthy subjects with epilepsy.

501  
502 **Effects of Felbatol® on Low-Dose Combination Oral Contraceptives:**  
503 A group of 24 nonsmoking, healthy white female volunteers established on an oral contraceptive regimen  
504 containing 30 µg ethinyl estradiol and 75 µg gestodene for at least 3 months received 2400 mg/day of  
505 felbamate from midcycle (day 15) to midcycle (day 14) of two consecutive oral contraceptive cycles.  
506 Felbamate treatment resulted in a 42% decrease in the gestodene AUC 0-24, but no clinically relevant  
507 effect was observed on the pharmacokinetic parameters of ethinyl estradiol. No volunteer showed  
508 hormonal evidence of ovulation, but one volunteer reported intermenstrual bleeding during felbamate  
509 treatment.

510  
511 **Drug/Laboratory Test Interactions:** There are no known interactions of Felbatol® with commonly used  
512 laboratory tests.

513  
514 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies were conducted in mice  
515 and rats. Mice received felbamate as a feed admixture for 92 weeks at doses of 300, 600, and 1200 mg/kg  
516 and rats were also dosed by feed admixture for 104 weeks at doses of 30, 100, and 300 (males) or 10, 30,  
517 and 100 (females) mg/kg. The maximum doses in these studies produced steady-state plasma  
518 concentrations that were equal to or less than the steady-state plasma concentrations in epileptic patients  
519 receiving 3600 mg/day. There was a statistically significant increase in hepatic cell adenomas in high-  
520 dose male and female mice and in high-dose female rats. Hepatic hypertrophy was significantly increased  
521 in a dose-related manner in mice, primarily males, but also in females. Hepatic hypertrophy was not  
522 found in female rats. The relationship between the occurrence of benign hepatocellular adenomas and the  
523 finding of liver hypertrophy resulting from liver enzyme induction has not been examined. There was a  
524 statistically significant increase in benign interstitial cell tumors of the testes in high-dose male rats  
525 receiving felbamate. The relevance of these findings to humans is unknown.

526  
527 As a result of the synthesis process, felbamate could contain small amounts of two known animal  
528 carcinogens, the genotoxic compound ethyl carbamate (urethane) and the nongenotoxic compound methyl  
529 carbamate. It is theoretically possible that a 50 kg patient receiving 3600 mg of felbamate could be  
530 exposed to up to 0.72 micrograms of urethane and 1800 micrograms of methyl carbamate. These daily

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531 doses are approximately 1/35,000 (urethane) and 1/5,500 (methyl carbamate) on a mg/kg basis, and  
532 1/10,000 (urethane) and 1/1,600 (methyl carbamate) on a mg/m<sup>2</sup> basis, of the dose levels shown to be  
533 carcinogenic in rodents. Any presence of these two compounds in felbamate used in the lifetime  
534 carcinogenicity studies was inadequate to cause tumors.

535  
536 Microbial and mammalian cell assays revealed no evidence of mutagenesis in the Ames *Salmonella*  
537 /microsome plate test, CHO/HGPRT mammalian cell forward gene mutation assay, sister chromatid  
538 exchange assay in CHO cells, and bone marrow cytogenetics assay.

539  
540 Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up  
541 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  
542 daily dose on a mg/m<sup>2</sup> basis.

543  
544 **Pregnancy: Pregnancy Category C.** The incidence of malformations was not increased compared to  
545 control in offspring of rats or rabbits given doses up to 13.9 times (rat) and 4.2 times (rabbit) the human  
546 daily dose on a mg/kg basis, or 3 times (rat) and less than 2 times (rabbit) the human daily dose on a  
547 mg/m<sup>2</sup> basis. However, in rats, there was a decrease in pup weight and an increase in pup deaths during  
548 lactation. The cause for these deaths is not known. The no effect dose for rat pup mortality was 6.9 times  
549 the human dose on a mg/kg basis or 1.5 times the human dose on a mg/m<sup>2</sup> basis.

550  
551 Placental transfer of felbamate occurs in rat pups. There are, however, no studies in pregnant women.  
552 Because animal reproduction studies are not always predictive of human response, this drug should be  
553 used during pregnancy only if clearly needed.

554  
555 To provide information regarding the effects of in utero exposure to Felbatol®, physicians are advised to  
556 recommend that pregnant patients taking Felbatol enroll in the NAAED Pregnancy Registry. This can be  
557 done by calling the toll free number 1-888-233-2334, and must be done by patients themselves.  
558 Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

559  
560 **Labor and Delivery:** The effect of felbamate on labor and delivery in humans is unknown.

561  
562 **Nursing Mothers:** Felbamate has been detected in human milk. The effect on the nursing infant is  
563 unknown (see **Pregnancy** section).

564  
565 **Pediatric Use:** The safety and effectiveness of Felbatol® in children other than those with Lennox-  
566 Gastaut syndrome has not been established.

567  
568 **Geriatric Use:** No systematic studies in geriatric patients have been conducted. Clinical studies of  
569 Felbatol® did not include sufficient numbers of patients aged 65 and over to determine whether they  
570 respond differently from younger patients. Other reported clinical experience has not identified  
571 differences in responses between the elderly and younger patients. In general, dosage selection for an  
572 elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the  
573 greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other  
574 drug therapy.

575  
576 **ADVERSE REACTIONS**

577 **To report SUSPECTED ADVERSE REACTIONS, contact Meda Pharmaceuticals Inc. at**  
578 **1-800-526-3840 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch) .**

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

584  
585 The most common adverse reactions seen in association with Felbatol® in children during adjunctive  
586 therapy are anorexia, vomiting, insomnia, headache, and somnolence.

587  
588 The dropout rate because of adverse experiences or intercurrent illnesses among adult felbamate patients  
589 was 12 percent (120/977). The dropout rate because of adverse experiences or intercurrent illnesses  
590 among pediatric felbamate patients was six percent (22/357). In adults, the body systems associated with  
591 causing these withdrawals in order of frequency were: digestive (4.3%), psychological (2.2%), whole  
592 body (1.7%), neurological (1.5%), and dermatological (1.5%). In children, the body systems associated  
593 with causing these withdrawals in order of frequency were: digestive (1.7%), neurological (1.4%),  
594 dermatological (1.4%), psychological (1.1%), and whole body (1.0%). In adults, specific events with an  
595 incidence of 1% or greater associated with causing these withdrawals, in order of frequency were:  
596 anorexia (1.6%), nausea (1.4%), rash (1.2%), and weight decrease (1.1%). In children, specific events  
597 with an incidence of 1% or greater associated with causing these withdrawals, in order of frequency was  
598 rash (1.1%).

599  
600 **Incidence in Clinical Trials:**

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

609  
610 **Adults**

611 **Incidence in Controlled Clinical Trials--Monotherapy Studies in Adults:**

612 The table that follows enumerates adverse events that occurred at an incidence of 2% or more among 58  
613 adult patients who received Felbatol® monotherapy at dosages of 3600 mg/day in double-blind controlled  
614 trials. Table 3 presents reported adverse events that were classified using standard WHO-based dictionary  
615 terminology.  
616

<b>Table 3 Adults Treatment-Emergent Adverse Event Incidence in Controlled Monotherapy Trials</b>		
	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

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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		

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**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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<b>Table 4 Adults Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials</b>		
	Felbatol <sup>®</sup>	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		
Sinusitis	5.3	7.0
Pharyngitis	3.5	0
	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.

<b>Table 5 Children Treatment-Emergent Adverse Event Incidence in Controlled Add-On Lennox-Gastaut Trials</b>		
	Felbatol®	Placebo
	(N=31)	(N=27)
Body System/Event	%	%
<b>Body as a Whole</b>		
Fever	22.6	11.1
Fatigue	9.7	3.7
Weight Decrease	6.5	0
Pain	6.5	0
<b>Central Nervous System</b>		
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
<b>Dermatological</b>		
Rash	9.7	7.4
<b>Digestive</b>		
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
<b>Hematologic</b>		
Purpura	12.9	7.4
Leukopenia	6.5	0
<b>Respiratory</b>		
Upper Respiratory Tract Infection	45.2	25.9
Pharyngitis	9.7	3.7
Coughing	6.5	0
<b>Special Senses</b>		
Otitis Media	9.7	0

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

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638 In the paragraphs that follow, the adverse clinical events, other than those in the preceding tables, that  
639 occurred in a total of 977 adults and 357 children exposed to Felbatol® (felbamate) and that are  
640 reasonably associated with its use are presented. They are listed in order of decreasing frequency.  
641 Because the reports cite events observed in open-label and uncontrolled studies, the role of Felbatol® in  
642 their causation cannot be reliably determined.  
643  
644 Events are classified within body system categories and enumerated in order of decreasing frequency  
645 using the following definitions: frequent adverse events are defined as those occurring on one or more  
646 occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100-1/1000  
647 patients; and rare events are those occurring in fewer than 1/1000 patients.  
648  
649 Event frequencies are calculated as the number of patients reporting an event divided by the total number  
650 of patients (N=1334) exposed to Felbatol®.  
651  
652 **Body as a Whole:** *Frequent:* Weight increase, asthenia, malaise, influenza-like symptoms; *Rare:*  
653 anaphylactoid reaction, chest pain substernal.  
654 **Cardiovascular:** *Frequent:* Palpitation, tachycardia; *Rare:* supraventricular tachycardia.  
655 **Central Nervous System:** *Frequent:* Agitation, psychological disturbance, aggressive reaction;  
656 *Infrequent:* hallucination, euphoria, suicide attempt, migraine.  
657 **Digestive:** *Frequent:* SGOT increased; *Infrequent:* esophagitis, appetite increased; *Rare:* GGT elevated.  
658 **Hematologic:** *Infrequent:* Lymphadenopathy, leukopenia, leukocytosis, thrombocytopenia,  
659 granulocytopenia; *Rare:* antinuclear factor test positive, qualitative platelet disorder, agranulocytosis.  
660 **Metabolic/Nutritional:** *Infrequent:* Hypokalemia, hyponatremia, LDH increased, alkaline phosphatase  
661 increased, hypophosphatemia; *Rare:* creatinine phosphokinase increased.  
662 **Musculoskeletal:** *Infrequent:* Dystonia.  
663 **Dermatological:** *Frequent:* Pruritus; *Infrequent:* urticaria, bullous eruption; *Rare:* buccal mucous  
664 membrane swelling, Stevens-Johnson Syndrome.  
665 **Special Senses:** *Rare:* Photosensitivity allergic reaction.  
666  
667 **Postmarketing Adverse Event Reports:**  
668 Voluntary reports of adverse events in patients taking Felbatol® (usually in conjunction with other drugs)  
669 have been received since market introduction and may have no causal relationship with the drug(s). These  
670 include the following by body system:  
671 **Body as a Whole:** neoplasm, sepsis, L.E. syndrome, SIDS, sudden death, edema, hypothermia, rigors,  
672 hyperpyrexia.  
673 **Cardiovascular:** atrial fibrillation, atrial arrhythmia, cardiac arrest, torsade de pointes, cardiac failure,  
674 hypotension, hypertension, flushing, thrombophlebitis, ischemic necrosis, gangrene, peripheral ischemia,  
675 bradycardia, Henoch-Schönlein purpura (vasculitis).  
676 **Central & Peripheral Nervous System:** delusion, paralysis, mononeuritis, cerebrovascular disorder,  
677 cerebral edema, coma, manic reaction, encephalopathy, paranoid reaction, nystagmus, choreoathetosis,  
678 extrapyramidal disorder, confusion, psychosis, status epilepticus, dyskinesia, dysarthria, respiratory  
679 depression, apathy, concentration impaired.  
680 **Dermatological:** abnormal body odor, sweating, lichen planus, livedo reticularis, alopecia, toxic  
681 epidermal necrolysis.  
682 **Digestive:** (Refer to **WARNINGS** ) hepatitis, hepatic failure, G.I. hemorrhage, hyperammonemia,  
683 pancreatitis, hematemesis, gastritis, rectal hemorrhage, flatulence, gingival bleeding, acquired megacolon,  
684 ileus, intestinal obstruction, enteritis, ulcerative stomatitis, glossitis, dysphagia, jaundice, gastric ulcer,  
685 gastric dilatation, gastroesophageal reflux.  
686 **Fetal Disorders:** fetal death, microcephaly, genital malformation, anencephaly, encephalocele.  
687 **Hematologic:** (Refer to **WARNINGS** ) increased and decreased prothrombin time, anemia, hypochromic  
688 anemia, aplastic anemia, pancytopenia, hemolytic uremic syndrome, increased mean corpuscular volume

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689 (mcv) with and without anemia, coagulation disorder, embolism-limb, disseminated intravascular  
690 coagulation, eosinophilia, hemolytic anemia, leukemia, including myelogenous leukemia, and lymphoma,  
691 including T-cell and B-cell lymphoproliferative disorders.

692 **Metabolic/Nutritional:** hypernatremia, hypoglycemia, SIADH, hypomagnesemia, dehydration,  
693 hyperglycemia, hypocalcemia.

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

695 **Respiratory:** dyspnea, pneumonia, pneumonitis, hypoxia, epistaxis, pleural effusion, respiratory  
696 insufficiency, pulmonary hemorrhage, asthma.

697 **Special Senses:** hemianopsia, decreased hearing, conjunctivitis.

698 **Urogenital:** menstrual disorder, acute renal failure, hepatorenal syndrome, hematuria, urinary retention,  
699 nephrosis, vaginal hemorrhage, abnormal renal function, dysuria, placental disorder.

700

## 701 **DRUG ABUSE AND DEPENDENCE**

702 **Abuse:** Abuse potential was not evaluated in human studies.

703

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

707

## 708 **OVERDOSAGE**

709 Four subjects inadvertently received Felbatol® (felbamate) as adjunctive therapy in dosages ranging from  
710 5400 to 7200 mg/day for durations between 6 and 51 days. One subject who received 5400 mg/day as  
711 monotherapy for 1 week reported no adverse experiences. Another subject attempted suicide by ingesting  
712 12,000 mg of Felbatol® in a 12-hour period. The only adverse experiences reported were mild gastric  
713 distress and a resting heart rate of 100 bpm. No serious adverse reactions have been reported.

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

716

## 717 **DOSAGE AND ADMINISTRATION**

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

722

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

728

### 729 **Adults (14 years of age and over)**

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

732

733 **Monotherapy:** (Initial therapy) Felbatol® (felbamate) has not been systematically evaluated as initial  
734 monotherapy. Initiate Felbatol® at 1200 mg/day in divided doses three or four times daily. The prescriber  
735 is advised to titrate previously untreated patients under close clinical supervision, increasing the dosage in  
736 600-mg increments every 2 weeks to 2400 mg/day based on clinical response and thereafter to 3600  
737 mg/day if clinically indicated.

738

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739 **Conversion to Monotherapy:** Initiate Felbatol® at 1200 mg/day in divided doses three or four times  
740 daily. Reduce the dosage of concomitant AEDs by one-third at initiation of Felbatol® therapy. At week 2,  
741 increase the Felbatol® dosage to 2400 mg/day while reducing the dosage of other AEDs up to an  
742 additional one-third of their original dosage. At week 3, increase the Felbatol® dosage up to 3600 mg/day  
743 and continue to reduce the dosage of other AEDs as clinically indicated.  
744

745 **Adjunctive Therapy:** Felbatol® should be added at 1200 mg/day in divided doses three or four times  
746 daily while reducing present AEDs by 20% in order to control plasma concentrations of concurrent  
747 phenytoin, valproic acid, phenobarbital, and carbamazepine and its metabolites. Further reductions of the  
748 concomitant AEDs dosage may be necessary to minimize side effects due to drug interactions. Increase  
749 the dosage of Felbatol® by 1200 mg/day increments at weekly intervals to 3600 mg/day. Most side  
750 effects seen during Felbatol® adjunctive therapy resolve as the dosage of concomitant AEDs is  
751 decreased.  
752

Table 6 Dosage Table (adults)			
Dosage reduction of concomitant AEDs	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
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.

753  
754 While the above Felbatol® conversion guidelines may result in a Felbatol® 3600 mg/day dose within 3  
755 weeks, in some patients titration to a 3600 mg/day Felbatol® dose has been achieved in as little as 3 days  
756 with appropriate adjustment of other AEDs.  
757

#### 758 **Children with Lennox-Gastaut Syndrome (Ages 2-14 years)**

759 **Adjunctive Therapy:** Felbatol® should be added at 15 mg/kg/day in divided doses three or four times  
760 daily while reducing present AEDs by 20% in order to control plasma levels of concurrent phenytoin,  
761 valproic acid, phenobarbital, and carbamazepine and its metabolites. Further reductions of the  
762 concomitant AEDs dosage may be necessary to minimize side effects due to drug interactions. Increase  
763 the dosage of Felbatol® by 15 mg/kg/day increments at weekly intervals to 45 mg/kg/day. Most side  
764 effects seen during Felbatol® adjunctive therapy resolve as the dosage of concomitant AEDs is  
765 decreased.  
766

#### 767 **HOW SUPPLIED**

768 Felbatol® (felbamate) Tablets, 400 mg, are yellow, scored, capsule-shaped tablets, debossed 0430 on one  
769 side and FELBATOL 400 on the other; available in bottles of 100 (NDC 0037-0430-01). Felbatol®  
770 (felbamate) Tablets, 600 mg, are peach-colored, scored, capsule-shaped tablets, debossed 0431  
771 on one side and FELBATOL 600 on the other; available in bottles of 100 (NDC 0037-0431-01).  
772 Felbatol® (felbamate) Oral Suspension, 600 mg/5 mL, is peach-colored; available in 8 oz bottles (NDC  
773 0037-0442-67) and 32 oz bottles (NDC 0037-0442-17).  
774

775 Shake suspension well before using. Store at controlled room temperature 20°-25°C (68°-77°F). Dispense  
776 in tight container.  
777

778 **To report SUSPECTED ADVERSE REACTIONS, contact Meda Pharmaceuticals Inc. at**  
779 **1-800-526-3840 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

780  
781 MEDA Pharmaceuticals®

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782 MEDA Pharmaceuticals Inc.  
783 Somerset, NJ 08873  
784 IN-00431-18 Rev. 7/11

785  
786 **PATIENT/PHYSICIAN ACKNOWLEDGMENT FORM**

787  
788 FELBATOL® (felbamate) SHOULD NOT BE USED BY PATIENTS UNTIL THERE HAS BEEN A  
789 COMPLETE DISCUSSION OF THE RISKS.

790 All patients treated with Felbatol should acknowledge that they understand the risks and other information  
791 about Felbatol discussed below, and physicians should acknowledge this discussion.

792  
793 **IMPORTANT INFORMATION AND WARNING:**

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

796  
797 **PATIENT ACKNOWLEDGMENT:**

798  
799 **Do not sign this form if there is anything you do not understand about the information you**  
800 **have received. Ask your doctor about anything you do not understand before you initial**  
801 **any of the items below or sign this form.**

802  
803 My [My son, daughter, ward \_\_\_\_\_]'s]  
804 treatment with Felbatol® has been personally explained to me by Dr. \_\_\_\_\_.  
805 The following points of information, among others, have been specifically discussed and made clear and I  
806 have had the opportunity to ask any questions concerning this information:

807  
808 1. I, \_\_\_\_\_ (Patient's Name),  
809 understand that Felbatol® is used to treat certain types of seizures and my physician has told me that I  
810 have this type(s) of seizures;  
811 INITIALS: \_\_\_\_\_

812  
813 2. I understand that Felbatol® is being used because my seizures have not been satisfactorily treated with  
814 other antiepileptic drugs;  
815 INITIALS: \_\_\_\_\_

816  
817 3. I understand that there is a serious risk that I could develop aplastic anemia and/or liver failure, both of  
818 which are potentially fatal, by using Felbatol®;  
819 INITIALS: \_\_\_\_\_

820  
821 4. I understand that there are no laboratory tests which will predict if I am at an increased risk for one of  
822 the potentially fatal conditions;  
823 INITIALS: \_\_\_\_\_

824  
825 5. I understand that I should have the recommended blood work before my treatment with Felbatol® is  
826 begun (baseline) and periodically thereafter as clinical judgement warrants. I understand that although this  
827 blood work may help detect if I develop one of these conditions, it may do so only after significant,  
828 irreversible and potentially fatal damage has already occurred;  
829 INITIALS: \_\_\_\_\_

830

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

836  
837 7. I understand that I must immediately report any unusual symptoms to Dr. \_\_\_\_\_  
838 and be especially aware of any rashes, easy bruising, bleeding, sore throats, fever, and/or dark urine;  
839 INITIALS: \_\_\_\_\_

840  
841 8. I understand that antiepileptic drugs such as Felbatol® may increase the risk of suicidal thoughts and  
842 behavior. I understand that I must immediately report any unusual changes in mood or behavior,  
843 symptoms of depression or thoughts about self-harm to Dr. \_\_\_\_\_.  
844 INITIALS: \_\_\_\_\_

845  
846  
847 \_\_\_\_\_

848 **Patient, Parent, or Guardian**

849  
850 \_\_\_\_\_

850 **Address**

851 \_\_\_\_\_

852 **Telephone**

853 \_\_\_\_\_

854 **PHYSICIAN STATEMENT:**

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

860 \_\_\_\_\_  
861 Physician Date

862

863 Revised: 7/11

864

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

867

868 **SUPPLY OF PATIENT/PHYSICIAN ACKNOWLEDGMENT FORMS:**

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

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874



875

876