Core Safety Profile

Active substance: Felbamate
Pharmaceutical form(s)/strength: 400 and 600 mg, tablets
600mg/5ml, oral suspension
P-RMS: FR/H/PSUR/0002/001
Date of FAR: 27.02.2013
4.2 Posology and method of administration

../Felbamate should be used only under the supervision of a neurologist or a pediatrician with expertise in the treatment of epilepsy.

LENNOX-GASTAUT SYNDROME

Dosage in adults and adolescents 14 years and older:

Adjunctive therapy with other antiepileptic agents: ../Felbamate administered in combination with carbamazepine, phenytoin, phenobarbital or valproic acid may increase the incidence of their characteristic adverse reactions (see section 4.5). Initiate ../Felbamate dosage at 600 mg to 1200 mg/day, administered in 2 or 3 divided doses. At onset of ../Felbamate therapy, reduce the dose of concomitant carbamazepine, phenytoin, phenobarbital, and/or valproic acid initially by 20% to 30%. ../Felbamate dosage may then be titrated in increments of 600 mg/day to 1200 mg/day at intervals of about one week to a maximum of 3600 mg/day administered in 3 or 4 divided doses. Dose adjustment of carbamazepine, phenytoin, phenobarbital, and valproic acid should be considered as ../Felbamate dose increases. However, interactions are dose-dependent and subject to individual patient variability. Therefore, all dose adjustments of concomitant antiepileptic medicines should be based not only on steady-state plasma concentrations but also on clinical observations.

Pediatric dosage: children 4 to 11 years old and adolescents 12 to 14 years old

Adjunctive therapy with other antiepileptic agents: ../Felbamate in combination with carbamazepine, phenytoin, phenobarbital, or valproic acid may increase the incidence of their characteristic adverse reactions (see section 4.5). Initiate ../Felbamate dosage at 7.5 mg/ kg/day to 15 mg/kg/day, administered in 2 or 3 divided doses. At onset of ../Felbamate therapy, reduce the dose of concomitant carbamazepine, phenytoin, phenobarbital, and/or valproic acid by 20% to 30% initially. At intervals of at least one week, ../Felbamate dosage may be titrated in 7.5 mg/kg to 15 mg/kg at increments to a maximum of 45 mg/kg/day (not to exceed 3600 mg/day) administered in 3 or 4 divided doses. Dose adjustment of carbamazepine, phenytoin, phenobarbital, and/or valproic acid should be considered as ../Felbamate dosage increases. However, interactions are dose-dependent and subject to individual patient variability. Therefore, all dose adjustments of concomitant antiepileptic medicines should be based not only on steady-state plasma concentrations but also on clinical observations.

Geriatric use: Based upon the limited clinical data in patients over 65 years old treated with ../Felbamate, no restrictions are necessary with regard to the elderly. In general, however, dosage titration for an elderly patient should be cautious.

Pediatric use: Safety and efficacy of ../Felbamate in children below the age of 4 years have not been established.

Dosage in patients with renal insufficiency: For patients with creatinine clearance < 50 ml/min, initial doses of ../Felbamate should be halved, and subsequent dose titration should be cautious.

Dosage in patients with hepatic dysfunction

Felbamate should not be used in patients with a history of hepatic dysfunction given the risk of hepatotoxicity (see section 4.3 and 4.4).

Food does not affect the rate and extent of absorption of felbamate.
4.3 Contraindications

/.../Felbamate is contraindicated in patients with:
- history of blood dyscrasia or hepatic dysfunction
- hypersensitivity to felbamate or to any of the excipients

4.4 Special warnings and precautions for use

**Information for patients:** Patients should be informed prior to initiation of the treatment that the use of /.../felbamate has been associated with aplastic anemia and hepatic failure, both potentially fatal conditions.

**Blood dyscrasias:** A number of serious hematologic adverse events, including thrombocytopenia, leucopenia, pancytopenia, anemia, and aplastic anemia have been reported in association with the use of /.../felbamate.

The most serious of these is aplastic anemia, which was fatal in 30% of cases. The incidence is estimated to be about one case per 4000 treated patients, which represents a large increase (100-fold greater) over the expected rate (2 to 5 per million of persons per year). Accordingly, /.../felbamate should only be used in patients with therapy refractory Lennox-Gastaut syndrome, when no alternative medical treatment is available.

The cases of aplastic anemia were discovered 2 to 12 months after the beginning of treatment with /.../felbamate. However, the injury to the bone marrow cells that is held to be ultimately responsible for the aplasia may occur weeks to months earlier. Accordingly, patients who are discontinued from /.../felbamate remain at risk for developing aplastic anemia for up to several months after discontinuation of the treatment. It is not known whether the risk of developing aplastic anemia changes with the duration of exposure. Consequently, it cannot be assumed that a patient who has been on /.../felbamate without signs of hematologic abnormality for long periods of time is without risk.

- A total blood cell count should be performed before the start of /.../felbamate treatment and every 2 weeks during treatment.

- If the results of blood cell count shows neutropenia (neutrophils <1500/mm³) and/or thrombocytopenia (platelets <150000/mm³), /.../felbamate should be discontinued and the patient should be investigated for possible aplastic anemia.

- A careful monitoring of clinical signs such as ecchymosis, petechia, bleeding or signs of infection and/or anemia (fatigue, weakness, etc.) should be performed. If such symptoms are present, a total blood cell count is to be performed immediately.

**Hepatotoxicity:** Severe cases of acute hepatic failure (resulting in fatalities in 30% of cases) have been reported in patients receiving /.../felbamate.

- Liver function tests (AST, ALT, bilirubin) should be performed before initiating /.../felbamate. Patients presenting abnormal liver function should not be treated with /.../felbamate.

- During treatment with /.../felbamate, liver function tests should be performed every 2 weeks. Patients developing clinically significant abnormal liver function should be withdrawn from /.../felbamate treatment.
Patients experiencing clinical signs or symptoms such as jaundice, anorexia, nausea, vomiting and abdominal pain should have liver function tests performed immediately.

Felbamate oral suspension contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Felbamate oral suspension contains methyl- and propylparahydroxybenzoates which may cause allergic reactions (possibly delayed).

Felbamate oral suspension contains less than 1 mmol sodium (2.9 mg) per 5 ml, i.e., essentially “sodium-free”.

Patients must be well hydrated while taking Felbamate, to reduce the likelihood of crystalluria, which has been reported very rarely.

**Hypersensitivity:**

- Felbamate should be used cautiously in those who have demonstrated hypersensitivity reactions to other carbamates.

- Severe hypersensitivity reactions, including anaphylactic shock, Stevens-Johnson syndrome, bullous eruption and epidermal necrolysis have been reported in connection with felbamate. These reactions typically occurred two to three weeks after the initiation of treatment. Symptoms included rash, fever, swelling of mucous membranes and anaphylaxis, leukopenia, thrombocytopenia, elevated liver function tests, arthralgia, myalgia and pharyngitis. In case of hypersensitivity to Felbamate, the drug should be discontinued and appropriate symptomatic therapy should be initiated.

**Withdrawal of Felbamate:** Antiepileptic agents including Felbamate should, in general, not be discontinued suddenly because of the possibility of increased seizure frequency. However, if the seriousness of the adverse event(s) justifies immediate discontinuation, this should be performed under close medical supervision. Patients in whom Felbamate has been discontinued due to serious adverse event(s) related to the drug should not be rechallenged.

**Increased frequency of convulsions:** As reported with other antiepileptic drugs some patients may experience an increase in seizure frequency or the onset of new types of seizures (see section 4.8). These phenomena may be the consequence of an overdosage, a decrease in plasma concentrations of concomitant antiepileptic treatment, or a paradoxical effect.

**Suicidal ideation and behaviour** have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for felbamate.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
4.5 Interaction with other medicinal products and other forms of interaction

Felbamate alters plasma concentrations of carbamazepine, phenytoin, phenobarbital, and valproic acid and/or their metabolites. To reduce the likelihood of possible adverse reactions due to drug interactions, carbamazepine, phenytoin, phenobarbital, and valproic acid dosage should be reduced as needed, based on clinical observation and steady-state plasma concentrations, if applicable (see section 4.2).

Effect of felbamate on other antiepileptic agents:

Carbamazepine: Felbamate decreases carbamazepine steady-state plasma concentration by approximately 25% while increasing carbamazepine epoxide levels by approximately 50%.

Phenytoin: Felbamate inhibits phenytoin's clearance in a dose-dependent manner. The phenytoin plasma concentration can increase by 20% to 60%.

Phenobarbital: Felbamate at a dose of 1200 mg BID increased phenobarbital AUC by approximately 25%.

Valproic acid: Felbamate at doses of 600 mg or 1200 mg BID increases valproate steady-state plasma concentration in a dose-dependent, linear manner. With the lower felbamate dose, mean valproate AUC and trough concentration increased by 28% and 18%, respectively; these values increased proportionately at the higher felbamate dose.

Clonazepam, oxcarbazepine, vigabatrin, and lamotrigine: Although felbamate at doses of 1200 mg every 12 hours produced statistically significant changes in the pharmacokinetics of clonazepam, lamotrigine and vigabatrin, these changes were minimal and of no clinical relevance. No changes were observed in the pharmacokinetics of the active monohydroxy metabolite of oxcarbazepine. Because a pharmacodynamic interaction of felbamate with any of these agents cannot be excluded, dosage adjustment should always be based on clinical response and tolerability.

Effects of other antiepileptic agents on felbamate:

Carbamazepine/Phenytoin/Phenobarbital: When carbamazepine or phenytoin is co-administered with felbamate, reduction in steady-state felbamate plasma concentrations may approach 20%. Phenobarbital coadministration causes about 35% reduction in felbamate steady-state trough concentrations.

Valproic acid: Valproic acid appears to have minimal effect on felbamate clearance; however, in one study, felbamate trough concentrations were approximately 50% higher than those achieved with /.../felbamate monotherapy.

Interactions between felbamate and non-antiepileptic agents:

Oral contraceptives: Felbamate reduced gestodene AUC by 42% and ethinyl estradiol AUC by 13% in females treated with a low-dose combination oral contraceptive. Efficacy and tolerance of oral contraceptives might be altered. Other combinations have not been studied.

Effect of felbamate on cytochrome P450:

Felbamate appears to be both an inhibitor and a mild activator of cytochrome P-450 in man. Therefore, the possibility of interactions with drugs metabolized by this hepatic enzyme system cannot be excluded. It has been shown that felbamate is a substrate for CYP3A4 and CYP2E1, but inhibition of these minor pathways has no expected pharmacokinetic consequences.
4.6 Pregnancy and lactation

**Pregnancy:** The safety of this medicinal product for use in human pregnancy has not been established.

Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm of the foetus due to felbamate, however, placental transfer of felbamate occurs. Because of animal reproduction studies are not always predictive of human response, and because of the potential for foetal bone marrow suppression, /.../felbamate should not be used during pregnancy.

**Lactation:** Felbamate is excreted in human milk. Because of a potential risk of /.../felbamate-induced bone marrow suppression in children receiving breast milk, /.../felbamate should not be given to mothers who are breast feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients may experience dizziness or drowsiness and should be cautioned against engaging in potentially dangerous activities.

4.8 Undesirable effects

/.../Felbamate is associated with an increased incidence of blood dyscrasias (see section 4.4), including aplastic anemia. Other serious hematologic adverse events include rare cases of thrombocytopenia, leucopenia, neutropenia, anemia, or combinations of these, including pancytopenia. Some of these occurred as part of an acute hypersensitivity reaction (see section 4.4). Some cases of severe hepatitis, including acute hepatic failure resulting in death have been reported with felbamate (see section 4.4).

Undesirable effects reported in adults patients treated with /.../felbamate adjunctive therapy during clinical studies and considered therapy related are listed in the following table, per system organ class and per frequency.

<table>
<thead>
<tr>
<th>Table 1 : Treatment related undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and the lymphatic system disorders</strong></td>
</tr>
<tr>
<td>Rare: Thrombocytopenia, leukopenia, neutropenia, anemia, or combinations of these, including pancytopenia, blood dyscrasias (see section 4.4), including aplastic anemia</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
</tr>
<tr>
<td>Rare: Anaphylactic shock (see section 4.4)</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
</tr>
<tr>
<td>Common: Weight decrease, anorexia</td>
</tr>
<tr>
<td>Uncommon: Hypophosphatemia</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
</tr>
<tr>
<td>Uncommon: Speech disorder, depression, stupor, anxiety</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td>Common: Insomnia, somnolence, ataxia, dizziness, headache</td>
</tr>
<tr>
<td>Rare: Seizure frequency increased (see section 4.4)</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
</tr>
</tbody>
</table>

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Common: Diplopia, abnormal vision

**Gastrointestinal disorders**
Common: Nausea, vomiting, dyspepsia, abdominal pain
Very rare: Constipation

**Hepatobiliary disorders**
Very rare: Hepatitis, severe; hepatic failure, acute (sometimes fatal) (see section 4.4)

**Skin & subcutaneous tissue disorders**
Uncommon: Rash, Hypersensitivity reactions (including Stevens-Johnson syndrome, bullous eruption, toxic epidermal necrolysis) (see section 4.4)
Rare: Crystalluria

**Renal and urinary disorders**
Very rare: Crystalluria

**General disorders and administration site conditions**
Uncommon: Abnormal gait, Fatigue

Children demonstrated a similar side effect pattern. Additionally, upper respiratory tract infections have been observed frequently in children; however, relationship to treatment is not probable.

### 4.9 Overdose

During the clinical program, patients who received inadvertent overdoses of felbamate ranging from 4000 to 12000 mg/day as part of adjunctive therapy or as monotherapy experienced adverse events that were mild to moderate in severity. Included were dizziness, constipation, purpura, headache, nausea, vomiting, weight decrease, fever, otitis media, somnolence and mild tachycardia (100 bpm).

As part of the post-marketing experience, overdoses of up to 40000 mg of felbamate were reported. The vast majority of the patients recovered uneventfully. Adverse events included ataxia, nystagmus, diplopia, agitation, crystalluria, or coma. Fatalities have been reported in patients who took overdoses of multiple agents including /.../felbamate.

If overdose occurs, general supportive measures should be employed. It is not known if felbamate is dialyzable.