Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for felbamate, the scientific conclusions are as follows:

The PRAC reviewed the available data regarding the risk of malformations and the neurodevelopmental risk following in utero exposure to felbamate, and agreed that taking into account the particular risk of haematotoxicity and hepatotoxicity changes to the Product Information were considered necessary to inform about use in pregnancy and lactation.

Clinical data related to felbamate in utero exposure is sparse, not allowing to draw any conclusion with regards on these malformative and neurodevelopmental risks, however In view of the particular felbamate toxicity, and considering data from spontaneous post-marketing reporting, the PRAC considered that changes to the product information as follows were necessary to inform healthcare professionals and patients:

- that women of childbearing potential use effective contraception during treatment and are informed of the necessity to plan pregnancy. Moreover, felbamate treatment resulted in a 42% decrease in the gestodene AUC, and 13% ethinylestradiol AUC, which should be considered in the choice of effective contraception in case of treatment with felbamate;
- to reassess the necessity of the antiepileptic treatment when a woman plans a pregnancy and in case of pregnancy;
- due to placental transfer, to further strengthen statements on potential haematotoxicity, but also the potential risk of hepatotoxicity in the fetus.
- to strengthen the information about excretion of felbamate in breast milk.
- to state that in case where the treatment should be maintained during pregnancy to fully inform the patient, and to use the minimal effective dose.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for felbamate the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing felbamate is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing felbamate are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.6

This section should be revised as follows:

Women of childbearing potential

Women of childbearing potential have to use an effective contraception during treatment and up to 1 month after end of treatment (see section 4.5).

Pregnancy

Risk related to epilepsy and antiepileptic drugs in general:

Specialist advice should be given to women who are of childbearing potential. The need for treatment with antiepileptic drugs should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of antiepileptic drug therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

Monotherapy using the minimal effective dose should be preferred whenever possible because therapy with multiple antiepileptic drugs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.

Risk related to felbamate:

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 to the fetus due to felbamate, however, placental transfer of felbamate occurs **(see section 5.3).**

Because animal reproduction studies are not always predictive of human response, and because of the potential for fetal bone marrow suppression **and hepatotoxicity,** felbamate should not be used ~~during pregnancy~~ **in women of childbearing potential not using effective contraception and in pregnant women, unless clearly necessary.**

Lactation

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

Package Leaflet

Section 2 - Take special care with felbamate

A warning should be added as follows:

[…]

If you are a woman of childbearing potential you will have to use an effective contraception during treatment and up to 1 month after end of treatment. Felbamate therapy may decrease the effectiveness of oral contraceptives, therefore another effective method should be used.

Section 2 - Pregnancy and breast-feeding

This section should be revised as follows:

Felbamate should not be used during pregnancy**, unless clearly necessary. If you are a woman of childbearing potential you should use an effective contraception during treatment and up to 1 month after end of treatment. Felbamate therapy may decrease the effectiveness of oral contraceptives, therefore another effective method should be used.**

If you are pregnant or planning to become pregnant, ~~your doctor will advise whether you should continue to take felbamate~~ **consult your doctor promptly, you should not stop taking your medicine until you have discussed this with your doctor. Your doctor could decide to change your treatment.**

Felbamate is not recommended to mothers who are breast feeding. **Felbamate passes into breast milk. It can harm your baby especially with blood or hepatic injuries.**

If you are pregnant or breastfeeding, if you think you may be pregnant or if you are planning a pregnancy, ask your doctor or pharmacist for advice before taking this medicine.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	5 August 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	4 October 2017