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 PSURs for carbamazepine the scientific conclusions are as follows:

Interaction with brivaracetam

In view of available data on interaction with brivaracetam from the literature and information included in the brivaracetam product information, the PRAC concluded that the product information of products containing carbamazepine should be amended to reflect the interaction between carbamazepine and brivaracetam.

Hyperammonaemia

In view of available data on hyperammonaemia from the literature and spontaneous reports, including in some cases absence of relevant medical history, plausible time-to-onset, positive de-challenge and/or re-challenge, the PRAC considers that a causal relationship between carbamazepine and hyperammonaemia is at least a reasonable possibility. The PRAC concluded that the product information of products containing carbamazepine should be amended accordingly.

Use during pregnancy and in women of childbearing potential

In view of available data on use during pregnancy and in women of childbearing potential from the literature, non-interventional studies (including registries) and spontaneous reports, the PRAC concluded that the product information of products containing carbamazepine, which do not have similar wordings, should be amended to reflect information on the risks associated with use during pregnancy, the need for effective contraception and counselling in women of childbearing potential and the potential for interaction with hormonal contraception potentially leading to lack of efficacy.

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 carbamazepine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing carbamazepine 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 carbamazepine 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 4.4

The information should be included or updated as follows:

Women of childbearing potential

Carbamazepine may cause foetal harm when administered to a pregnant woman. Prenatal exposure to carbamazepine may increase the risks for major congenital malformations and other adverse development outcomes (see Section 4.6).

Carbamazepine should not be used in women of childbearing potential unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

Women of childbearing potential should be fully informed of the potential risk to the foetus if they take carbamazepine during pregnancy.

Before the initiation of treatment with carbamazepine in a woman of childbearing potential, pregnancy testing should be considered.

Women of childbearing potential should use effective contraception during treatment and for two weeks after stopping treatment. Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see Sections 4.5 and 4.6).

Women of childbearing potential should be counselled regarding the need to consult her physician as soon as she is planning pregnancy to discuss switching to alternative treatments prior to conception and before contraception is discontinued (see Section 4.6).

Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant and is taking carbamazepine.

- Section 4.5

The interactions section should be amended as follows:

Agents that may raise the active metabolite carbamazepine-10,11-epoxide plasma levels:

[…]

Since raised plasma carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of <carbamazepine or product name> should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Antiepileptics: progabide, valproic acid, valnoctamide, valpromide, primidone, ***brivaracetam.***

- Section 4.6

The information should be included or updated as follows:

Pregnancy

Risk related to antiepileptic medicinal products in general

Specialist medical advice regarding the potential risks to a foetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant.

Sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as this may lead to seizures that could have serious consequences for the woman and the unborn child.

Monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

Risks related to carbamazepine

X crosses the placenta in humans. Prenatal exposure to carbamazepine may increase the risks for congenital malformations and other adverse developmental outcomes. In humans, carbamazepine exposure during pregnancy is associated with a frequency of major malformations 2 to 3 times higher than that of the general population, which has a frequency of 2-3%. Malformations such as neural tube defects (spina bifida), craniofacial defects such as cleft lip/palate, cardiovascular malformations, hypospadias, hypoplasia of the fingers, and other anomalies involving various body systems, have been reported in the offspring of women who used carbamazepine during pregnancy. Specialised antenatal surveillance for these malformations is recommended. Neurodevelopmental disorder has been reported among children born to women with epilepsy who used carbamazepine alone or in combination with other AEDs during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to carbamazepine during pregnancy are contradictory and a risk cannot be excluded.

Carbamazepine should not be used during pregnancy unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risks of taking carbamazepine during pregnancy.

Evidence suggest that the risk of malformation with carbamazepine may be dose-dependent. If based on a careful evaluation of the risks and the benefits, no alternative treatment option is suitable, and treatment with carbamazepine is continued, monotherapy and the lowest effective dose of carbamazepine should be used and monitoring of plasma levels is recommended. The plasma concentration could be maintained in the lower side of the therapeutic range 4 to 12 micrograms/mL provided seizure control is maintained.

Some antiepileptic drugs, such as carbamazepine, have been reported to decrease serum folate levels. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation is recommended before and during pregnancy. In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K1 be given to the mother during the last weeks of pregnancy as well as to the neonate.

If a woman is planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If a woman becomes pregnant while taking carbamazepine, she should be

referred to a specialist to reassess carbamazepine treatment and consider alternative treatment options.

[…]

Women of childbearing potential

Carbamazepine should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risk of potential harm to the foetus if carbamazepine is taken during pregnancy and therefore the importance of planning any pregnancy. Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with carbamazepine.

Women of childbearing potential should use effective contraception during treatment and for two weeks after stopping treatment. Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives (see section 4.5), therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods. At least one effective method of contraception (such as an intra-uterine device) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, involving the patient in the discussion, when choosing the contraception method.

- Section 4.8

The following adverse reaction should be added under the SOC Metabolism and nutrition disorders with frequency *not known*:

Hyperammonaemia

Package Leaflet

- Section 2

Subsection: "Warnings and precautions"

…

There is a risk of harm to the unborn child if X is used during pregnancy. Women of childbearing age should use effective contraception during treatment with X and for two weeks after the last dose (see Pregnancy and breast-feeding).

…

Subsection "Other medicines and X"

…

Hormonal contraceptives, e.g. pills, patches, injections or implants.

X may affect how hormonal contraceptives work and make them less effective at preventing pregnancy. Talk to your doctor, who will discuss with you the most suitable type of contraception to use while you are taking X.

Subsection "Pregnancy, breastfeeding and fertility"

X can cause major birth defects. If you take X during pregnancy your baby has up to 3 times the risk of having a birth defect than women not taking an antiepileptic medication. Major birth defects including neural tube defect (opening in the spine), birth defect of the face such as cleft of the upper lip and palate, birth defect of the head, heart defects, birth defect of the penis involving the urinary opening (hypospadias) and finger defects have been reported. Your unborn baby should be closely monitored if you have taken X while pregnant.

Problems with neurodevelopment (development of the brain) have been reported in babies born to mothers who used X during pregnancy. Some studies have shown that carbamazepine negatively affects neurodevelopment of children exposed to carbamazepine in the womb, while other studies have not found such an effect. The possibility of an effect on neurodevelopment cannot be ruled out.

If you are a woman of childbearing age and are not planning a pregnancy, you should use effective contraception during treatment with X. X may affect how hormonal contraceptives, such as the contraceptive (birth control) pill, work and make them less effective at preventing pregnancy. Talk to your doctor, who will discuss with you the most suitable type of contraception to use while you are taking X. If treatment with X is discontinued you should continue using effective contraception for two more weeks following discontinuation.

If you are a woman of childbearing age and are planning a pregnancy, talk to your doctor before you stop contraception and before you become pregnant about switching to other suitable treatments in order to avoid exposing the unborn baby to carbamazepine.

If you are or think you might be pregnant, tell your doctor straight away. You should not stop taking your medicine until you have discussed this with your doctor. Stopping your medication without consulting your doctor could cause seizures which could be dangerous to you and your unborn child. Your doctor may decide to change your treatment.

If you take X during pregnancy, your baby is also at risk for bleeding problems right after birth. Your doctor may give you and your baby a medicine to prevent this.

Subsection "Other medicines and X"

[…]

Other medicines for epilepsy […] **brivaracetam.**

- Section 4

Not known (frequency cannot be estimated from the available data):

high levels of ammonia in the blood (hyperammonaemia). The symptoms of hyperammonaemia may include irritability, confusion, vomiting, loss of appetite, and sleepiness.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	31 October 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 December 2021