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 phenytoin, the scientific conclusions are as follows:

Use during pregnancy and in women of childbearing potential

A meta-analysis was published within the interval which estimated the magnitude of risk of congenital malformations associated with use of phenytoin during pregnancy. The nature of the malformations that have been reported in association with use of phenytoin during pregnancy should be reflected in the product information based on currently available evidence. Available data pertaining to the risk of neurodevelopmental disorders following in utero exposure to phenytoin was also reviewed and, although the study findings are conflicting, a risk cannot be excluded, therefore, it was considered that the current evidence should be reflected in the SmPC. Furthermore, inclusion of a specific warning in section 4.4 of the SmPC for all phenytoin products in relation to use in women of childbearing potential is considered warranted in order to highlight important information on the risks associated with use during pregnancy and the need for effective contraception in women of childbearing potential and the potential for interaction with hormonal contraception potentially leading to lack of efficacy.

Update of sections 4.4 and 4.6 of the SmPC to add a warning on use in pregnancy and in women of childbearing potential. The Package leaflet is updated accordingly.

Genetic factors associated with risk of severe cutaneous adverse reactions and toxicity

In view of available data on an increased risk of severe cutaneous adverse reactions in carriers of the CYP2C9*3 allele and risk of increased toxicity in intermediate or poor metabolisers of CYP2C9 substrates from the literature, the Lead Member State concluded that the product information of products containing phenytoin should be amended accordingly.

Update of section 4.4 of the SmPC to add a warning on an increased risk of severe cutaneous adverse reactions in carriers of the CYP2C9*3 allele and risk of increased toxicity in intermediate or poor metabolisers of CYP2C9 substrates. The Package leaflet is updated accordingly.

Interaction with Direct Oral Anticoagulants

Based on published literature case reports describing interactions between phenytoin and dabigatran and phenytoin and rivaroxaban, and a mechanistic basis for an interaction leading to reduced plasma concentrations of direct oral anticoagulants, the Lead Member State considered that an update to the product information in alignment with the product information of direct oral anticoagulants authorised in the European Union is warranted.

Update of section 4.5 of the SmPC to add the interactions with direct oral anticoagulants. The Package leaflet is updated accordingly.

Interaction with lacosamide

Based on data from pharmacokinetic studies which found that serum lacosamide concentrations were lowered by phenytoin and enzyme-inducing antiepileptic drugs, including phenytoin, and to align with the product information for lacosamide products authorised in the European Union, the Lead member State considered that a product information update was warranted.
Update of section 4.5 of the SmPC to add the interaction with lacosamide. The Package leaflet is updated accordingly.

Interaction with ticagrelor

In the context of a warning on CYP3A inducers in section 4.5 of the SmPC for Brilique (ticagrelor), reference to phenytoin is included as an example of a CYP3A inducer that would be expected to decrease the exposure to ticagrelor, potentially reducing its efficacy. Phenytoin is considered a strong inducer of CYP3A4, therefore, based on biological plausibility, it is considered that an update to the product information to reflect this interaction is warranted, in alignment with the product information for ticagrelor products authorised in the European Union.

Update of section 4.5 of the SmPC to add the interaction with ticagrelor. The Package leaflet is updated accordingly.

Interaction with valproate

Literature publications have identified an association between concomitant use of phenytoin with valproate/valproic acid and an increased risk of hyperammonaemia. A number of mechanisms have been hypothesised through which phenytoin may enhance the risk of hyperammonaemia associated with valproate. While the possibility of an interaction between phenytoin and valproate may be referred to in the product information for individual products, there is no specific reference to the possibility of hyperammonaemia occurring as a consequence of this interaction. The LMS considered that based on the data from the clinical studies and the plausible mechanisms which have been proposed, an update to the product information is warranted.

Update of section 4.5 of the SmPC to add the interaction between phenytoin and valproate.

Pure red cell aplasia

In view of available data on pure red cell aplasia from the literature and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge, the Lead Member State considers a causal relationship between phenytoin and pure red cell aplasia is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing phenytoin should be amended accordingly.

Update of section 4.8 of the SmPC to add the adverse reaction pure red cell aplasia with a frequency not known. The Package leaflet is updated accordingly.

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

[This update is needed for MAHs which do not have similar wordings (SmPC and PL)]

For oral phenytoin products:

- Section 4.4

A warning should be added as follows:

…

Women of childbearing potential

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

X 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.

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

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

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 phenytoin.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, X 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).

…

- Section 4.6

A warning should be added as follows:

Pregnancy

…

Phenytoin crosses the placenta in humans.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. In humans, phenytoin 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 orofacial clefts, cardiac defects, craniofacial defects, nail and digit hypoplasia, and growth abnormalities (including microcephaly and prenatal growth deficiency), have been reported either individually or as part of a Fetal Hydantoin Syndrome among children born to women with epilepsy who used phenytoin during pregnancy. Neurodevelopmental disorder has been reported among children born to women with epilepsy who used phenytoin alone or in combination with other AEDs during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded.

X 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 phenytoin during pregnancy.

If based on a careful evaluation of the risks and the benefits, no alternative treatment option is suitable, and treatment with X is continued, the lowest effective dose of phenytoin should be used. 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 phenytoin, she should be referred to a specialist to reassess phenytoin treatment and consider alternative treatment options.

Women of childbearing potential

X 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 phenytoin 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 X.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, X 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 section 4.5). 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.

…

For parenteral phenytoin products:

[This update is needed for MAHs which do not have similar wordings (SmPC and PL)]

- Section 4.4

…

Women of childbearing potential

Phenytoin may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for major congenital malformations and other adverse

development outcomes (see Section 4.6). The magnitude of the risk to the foetus is unknown when phenytoin use is of short duration (emergency situations).

X should not be used in women of childbearing potential except where there is a clinical need and when possible, the woman should be informed of the potential risk to the foetus associated with the use of phenytoin during pregnancy. In emergency situations, the risk of harm to the foetus should be assessed in view of the risk of [indication for use] for both the foetus and the pregnant woman.

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

Due to enzyme induction, X may result in a failure of the therapeutic effect of hormonal contraceptives (see Sections 4.5 and 4.6).

…

- Section 4.6

…

Phenytoin crosses the placenta in humans.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. In humans, phenytoin 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 orofacial clefts, cardiac defects, craniofacial defects, nail and digit hypoplasia, and growth abnormalities (including microcephaly and prenatal growth deficiency), have been reported either individually or as part of a Fetal Hydantoin Syndrome among children born to women with epilepsy who used phenytoin during pregnancy. Neurodevelopmental disorder has been reported among children born to women with epilepsy who used phenytoin alone or in combination with other AEDs during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded.

X should not be used during pregnancy except where there is a clinical need and when possible, the woman is made aware of the risk of potential harm to the foetus.

…

Package Leaflet

For oral phenytoin products

- 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 (see Pregnancy and breast-feeding).

…

Subsection “Pregnancy <and><,> 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 growth, skull, facial, nail, finger and heart abnormalities have been reported. Some of these may occur together as part of a fetal hydantoin syndrome.

Problems with neurodevelopment (development of the brain) have been reported in babies born to mothers who used phenytoin during pregnancy. Some studies have shown that phenytoin negatively affects neurodevelopment of children exposed to phenytoin 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 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 phenytoin.

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.

…

Package leaflet

For parenteral phenytoin products

- 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 (see Pregnancy <and><,> breastfeeding <and fertility>”).

…

Subsection “Pregnancy <and><,> 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 growth, skull, facial, nail, finger and heart abnormalities have been reported. Some of these may occur together as part of a fetal hydantoin syndrome.

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

…

For all formulations (i.e. for oral and parenteral phenytoin products)

Summary of Product Characteristics

- Section 4.4

…

Case-control, genome-wide association studies in Taiwanese, Japanese, Malaysian and Thai patients have identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant.

…

CYP2C9 metabolism

Phenytoin is metabolised by the CYP450 CYP2C9 enzyme. Patients who are carriers of the decreased function CYP2C9*2 or CYP2C9*3 variants (intermediate or poor metabolisers of CYP2C9 substrates) may be at risk of increased phenytoin plasma concentrations and subsequent toxicity. In patients who are known to be carriers of the decreased function CYP2C9*2 or *3 alleles, close monitoring of clinical response is advised and monitoring of plasma phenytoin concentrations may be required.

- Section 4.5

The interaction should be added as follows:

Concomitant administration of phenytoin and valproate has been associated with an increased risk of valproate-associated hyperammonaemia. Patients treated concomitantly with these two drugs should be monitored for signs and symptoms of hyperammonaemia.

…

Drugs whose serum levels and/or effects may be reduced by phenytoin

…

Oral anticoagulants (e.g. rivaroxaban, dabigatran, apixaban, edoxaban)

lacosamide

ticagrelor

- Section 4.8

The following adverse reaction should be added under the SOC Blood and lymphatic system disorders with a frequency not known:

Pure red cell aplasia

Package Leaflet

Section 2. What you need to know before you <take> <use> X

Subsection: “Warnings and precautions”

Talk to your doctor before <taking> <using> X

…

If you are of Taiwanese, Japanese, Malaysian or Thai origin and tests have shown that you carry the genetic variant CYP2C9*3.

Subsection: Other medicines and X

Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines.

…

- **anticoagulants e.g. rivaroxaban, dabigatran, apixaban, edoxaban**

- **lacosamide**

- **ticagrelor**

Section 4 Possible side effects

…

a decrease in the number of a type of red blood cell (pure red cell aplasia).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of the agreement

Adoption of CMDh agreement:	April 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the agreement:	6 June 2021
Implementation of the agreement by the Member States (submission of the variation by the Marketing Authorisation Holder):	5 August 2021