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 fosphenytoin, the scientific conclusions are as follows:

CYP2C9 variants
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 PRAC concluded that the product information of products containing fosphenytoin should be amended accordingly.

Interactions
The interactions between phenytoin with tenofovir alafenamide and afatinib are considered to be of clinical significance, in view of their therapeutic indications (HIV/Hepatitis B/ particular types of non-small cell lung cancer). Therefore, the PRAC agreed they should be reflected in the SmPC for phenytoin within the table 'Drugs whose serum levels and/or effects may be altered by phenytoin listed by likely mechanism'. An update to the PL is not considered necessary as the potential for interaction with medicines used to treat HIV and cancer is already reflected there.

Urticaria
In view of available data on urticaria from spontaneous reports including in some cases a close temporal relationship and a positive de-challenge, the Lead Member State considers a causal relationship between fosphenytoin and urticaria is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing fosphenytoin should be amended 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 fosphenytoin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing fosphenytoin 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 fosphenytoin 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~~)

CYP2C9 variants

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Serious Cutaneous Adverse Reactions

Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. **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.

Package Leaflet
Section 2

Warnings and Precautions
In the general population, serious skin side effects can rarely occur during treatment with <Product>; for signs and symptoms of serious skin reactions and what action to take please see section 4. In people of Chinese or Asian origin this risk may be associated with a variant in genes. If you are of **Chinese or Asian** ~~such~~ origin and tests have shown that you carry **the** ~~this~~ genetic variant ~~(~~HLA-B*1502~~)~~**, or if you are of Taiwanese, Japanese, Malaysian or Thai origin and tests have shown that you carry the genetic variant CYP2C9*3**, discuss this with your doctor before taking <Product>.

Interactions

Summary of Product Characteristics

- Section 4.5

Drugs whose serum levels and/or effects may be altered by phenytoin listed by likely mechanism:

Drug	Mechanism
tenofovir alafenamide	**P-glycoprotein induction**
afatinib	

Urticaria

Summary of Product Characteristics

- Section 4.8

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders with a frequency not known.

Urticaria

Package Leaflet
Section 4

Not known: frequency cannot be estimated from the available data

Hives

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	09 May 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	08 July 2021