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 lamotrigine, the scientific conclusions are as follows:

The brandleader MAH was requested to provide cumulative reviews on a rare, but very serious immune system reaction, hemophagocytic lymphohistiocytosis (HLH), caused by Lamictal following a safety alert published by the FDA. Following assessment of the responses, it was concluded that the signal of HLH should be included in sections 4.4 and 4.8 of the summary of product characteristics (SmPC) and the patient leaflet (PL) updated accordingly.

Following an ongoing signal of Brugada syndrome and a cumulative review of cases of Brugada syndrome provided by the brand leader MAH, it was shown that that the symptoms of Brugada syndrome may manifest when patients are exposed to lamotrigine. The PRAC therefore was of the view that the use of lamotrigine in patients with Brugada syndrome should preferably be avoided, and that the SmPC and the PL should be updated with the addition of a warning in section 4.4 of the SmPC, with corresponding changes to the PL.

A signal for hypogammaglobulinemia was also identified by a couple of Member States. Based on the available data, it was considered that there is reasonable evidence that causality between hypogammaglobulinemia and lamotrigine treatment is possible, and that hypogammaglobulinemia should be included in section 4.8 of the SmPC and the PL.

Based on new literature data, one of the Member States commented on the risk in case of exposure during breast-feeding, where adverse effects in breastfed children were reported in a publication during the period covered by the PSUR. Following assessment of the literature data, it was concluded that the wording in the SmPC and PL should be updated to include the risk of exposure during breast-feeding.

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 lamotrigine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing lamotrigine 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 lamotrigine 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 Special warnings and precautions for use

The following warnings for Brugada syndrome and Haemophagocytic lymphohistiocytosis (HLH) should be added as follows:

Brugada-type ECG

Arrhythmogenic ST-T abnormality and typical Brugada ECG pattern has been reported in patients treated with lamotrigine.The use of lamotrigine should be carefully considered in patients with Brugada syndrome.

Haemophagocytic lymphohistiocytosis (HLH)

HLH has been reported in patients taking lamotrigine (see section 4.8). HLH is characterised by signs and symptoms, like fever, rash, neurological symptoms, hepatosplenomegaly, lymphadenopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation, HLH can be life threatening.

Patients should be informed of the symptoms associated with HLH and should be advised to seek medical attention immediately if they experience these symptoms while on lamotrigine therapy.

Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. Lamotrigine should be promptly discontinued unless an alternative aetiology can be established.

- Section 4.6 Pregnancy and lactation (deletion, addition)

The following section should be amended:

Lactation

Lamotrigine has been reported to pass into breast milk in highly variable concentrations, resulting in total lamotrigine levels in infants of up to approximately 50% of the mother's. Therefore, in some breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur. ~~Among a limited group of. no adverse effects were observed.~~

The potential benefits of breast-feeding should be weighed against the potential risk of adverse effects occurring in the infant. Should a woman decide to breast-feed while on therapy with lamotrigine, the infant should be monitored for adverse effects, **such as sedation, rash and poor weight gain.**

- Section 4.8 Undesirable effects

The following adverse reaction(s) should be added under the SOC Blood and lymphatic disorders with a frequency of "very rare":

Table of ADRs

SOC Blood and lymphatic disorders

Very rare: **Haemophagocytic lymphohistiocytosis (HLH)**

SOC Immune system disorders

Unknown: **Hypogammaglobulinaemia**

Package Leaflet

Section 2: What you need to know before you take lamotrigine

The following should be included:

Warnings and precautions

Brugada syndrome

Brugada syndrome is a genetic disease that results in abnormal electrical activity within the heart. ECG abnormalities which may lead to arrhythmias (abnormal heart rhythm) can be triggered by lamotrigine. Talk to your doctor, if you have this condition.

Haemophagocytic lymphohistiocytosis (HLH)

There have been reports of a rare but very serious immune system reaction, in patients taking lamotrigine. Contact your doctor or pharmacist immediately if you experience any of the following symptoms while taking lamotrigine: fever, rash, neurological symptoms (e.g. shaking or tremor, confusional state, disturbances of brain function).

Pregnancy and breastfeeding

If you are breast-feeding or planning to breast-feed ask your doctor or pharmacist for advice before taking this medicine. The active ingredient of <<product name>> passes into breast milk and may affect your baby. Your doctor will discuss the risks and benefits of breast-feeding while you're taking lamotrgine, and will check your baby from time to time, whether drowsiness, rash or poor weight gain occurs, if you decide to breast-feed. Inform your doctor if you observe any of these symptomps in your baby.

- Section 4: Possible side effects

The following adverse events should be included:

Haemophagocytic lymphohistiocytosis (HLH) (see section 2 What you need to know before you take lamotrigine).

Lower immunity because of lower levels of antibodies called immunoglobulins in the blood which help protect against infection.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	08 September 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	07 November 2018