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:

HLA*B-15:02 allele as a predictor of SJS/TEN in patients with Asian origin treated with lamotrigine

Compared to previous published meta-analyses (Zeng et al (2015), Li et al (2014) and Cheung et al (2013)), the meta-analysis of Deng et al (2018) included four new case-control studies in Asian population resulting in larger pooled sample size and showed that HLA-B*1502 was detected in 15 of 54 (28%) LTG-induced SJS/TEN cases, and in 41 of 313 (13%) lamotrigine-tolerant controls. The meta-analysis resulted in an OR of 2.53 (1.25 - 5.13) in Asian population. Since for another antiepileptic drug carbamazepine per SmPC HLA-B*1502 testing in Asian population is advised before treatment initiation, information on the observed association of this allele also with lamotrigine induced SJS/TEN is considered informative for prescribers who may consider lamotrigine as alternative treatment to carbamazepine. The PI of lamotrigine should be updated with information on the increased risk of SJS/TEN in patients of Asian origin with HLA-B*1502.

Tics (motor and vocal tics)

Tics are known for lamotrigine (listed ADR) but can be further specified. Nine cases included six well documented case reports of tics including motor and vocal tics with lamotrigine (Angus leppan (2019)), and 3 cases by resp., Lombroso (1999), Seemuller (2006) and Alkin (2007). No clear mechanism of action could be determined although several mechanisms of actions have been suggested in literature including dopamine regulation, serotonin regulation or excitatory amino acids (EAAs) regulation.

Considering the available evidence from the cases reporting positive rechallenge and positive dechallenge and the dose-response relationship, a causal relationship between lamotrigine and tics including motor and vocal tics can be concluded. Since tics in general is included in the SmPC section 4.8 but in PIL only specified as motor tics, the MAHs of all lamotrigine containing products should update the product information with further characterisation of this ADR and reflect that tics can include motor and/or vocal tics.

Intravenous lipid (IVL) therapy in treatment of cardiotoxicity with lamotrigine overdose

Published case reports by Castanares et al (2012), Chavez et al (2015), and Sirianni et al (2008) report a positive effect of intravenous lipid therapy (IVL) on QRS widening in patients insufficiently responding to sodium bicarbonate. This positive effect is further supported by published reviews (Alyahya et al (2018), Cave el al (2009) Lee et al (2023)) and national toxicology/poison center monographs (Netherlands, Belgium and US) suggesting that IVL therapy may have a role in treatment of cardiotoxicity caused by certain lipophilic drugs. These reviews and monographs suggest that IVL therapy should not be used as a first-line therapy, but may be used if other treatments fail. Additional support is provided by the availability of several mechanisms of action that can explain the effectiveness of IVL in lamotrigine overdose, of which the lipid sink theory is considered most plausible. Additional another treatment strategy in the product information may contribute to improving the outcomes of lamotrigine overdose related cardiotoxicity. The LMS therefore recommends an update of the product information.

Pseudolymphoma

Considering two published case reports Reed et al 2019 (probable) and Kazemi et al 2022 (possible), the three spontaneous reports with causality assessed as "possible" and the known skin reactions, hypersensitivity and photoxic potential for lamotrigine as possible pathways for this event, there is sufficient evidence to conclude a causal relation between cutaneous pseudolymphoma and lamotrigine. The LMS therefore recommends an update of the product information.

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

A warning should be amended as follows:

Skin rash

[…]

Caution is also required when treating patients with a history of allergy or rash to other AEDs as the frequency of non-serious rash after treatment with lamotrigine was approximately three times higher in these patients than in those without such history.

HLA-B*1502 allele in individuals of Asian (primarily Han Chinese and Thai) origin has been shown to be associated with the risk of developing SJS/TEN when treated with lamotrigine. If these patients are known to be positive for HLA-B*1502, use of lamotrigine should be carefully considered.

- Section 4.8

The following adverse reaction(s) should be amended under the SOC Psychiatric disorders:

Tics **(motor and/or phonic tics)**

The following adverse reaction(s) should be amended under the SOC Blood and lymphatic system disorder with frequency "unknown":

Pseudolymphoma

- Section 4.9

The recommendations for overdose management should be amended as follows:

Treatment

In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Therapy aimed at decreasing absorption (activated charcoal) should be performed if indicated. Further management should be as clinically indicated, taking into account potential effects on cardiac conduction (see section 4.4). **Use of intravenous lipid therapy may be considered for treatment of cardiotoxicity that responds insufficiently to sodium bicarbonate.** There is no experience with haemodialysis as treatment of overdose. In six volunteers with kidney failure, 20% of the lamotrigine was removed from the body during a 4-hour haemodialysis session (see section 5.2).

Package Leaflet

2. What you need to know before you take <product>

[…]

Important information about potentially life-threatening reactions

A small number of people taking <product> get an allergic reaction or potentially life-threatening skin reaction, which may develop into more serious problems if they are not treated. These can include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). You need to know the symptoms to look out for while you are taking <product>. **This risk may be associated with a variant in genes in people from Asian origin (mainly Han Chinese and Thai). If you are of such origin and have been tested previously carrying this genetic variant (HLA-B* 1502), discuss this with your doctor before taking <product>.**

4. Possible side effects

[…]

Very rare side effects

These may affect up to 1 in 10,000 people:

• uncontrollable **repeated** body movements **and/or sounds or words** (*tics*), uncontrollable muscle spasms affecting the eyes, head and torso (*choreoathetosis*), or other unusual body movements such as jerking, shaking or stiffness

Other side effects

- **red nodules or patches on the skin (pseudolymphoma)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 20203 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	03 September 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	02 November 2023