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 amitriptyline, amitriptyline / amitriptylinoxide, amitriptylinoxide, the scientific conclusions are as follows:

In view of available data on **Drug reaction with eosinophilia and systemic symptoms (DRESS)** from the literature, spontaneous reports, including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge, and in view of a plausible mechanism of action, assessors consider a causal relationship between the aforementioned events and Amitriptyline is at least a reasonable possibility. Therefore, the PRAC concluded that the product information of products containing amitriptyline, amitriptyline/ amitriptylinoxide, amitriptylinoxide should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for amitriptyline, amitriptyline / amitriptylinoxide, amitriptylinoxide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing amitriptyline, amitriptyline / amitriptylinoxide, amitriptylinoxide is unchanged subject to the proposed changes to the product information.

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

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~~)

DRESS

Summary of Product Characteristics

4.4 Special warnings and precautions for use

……..

Severe cutaneous reactions

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with amitriptyline treatment. Most of these reactions occurred within 2 to 6 weeks.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for cutaneous reactions.

If signs and symptoms suggestive of these reactions appear, <medicine> should be withdrawn immediately, treatment with <medicine> must not be restarted in this patient at any time and, an alternative treatment should be considered (as appropriate).

Section 4.8 Undesirable Effects

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

Summary of safety profile:

Severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported in association with amitriptyline (see section 4.4)

Table of ADRs

Skin and subcutaneous tissue disorders SOC: Frequency: not known

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Package leaflet

Section 2 –

Warnings and precautions - Take special care with <product name>:

Serious cutaneous reactions including drug reaction with eosinophilia and systemic symptoms

(DRESS) have been reported in association with <medicine> treatment. Stop using <medicine> and seek medical attention immediately if you notice any of the symptoms related to these serious cutaneous reactions described in section 4.

- Section 4 Possible side Effects

Frequency not known:

Stop using <medicine> and seek medical attention immediately if you notice any of the following symptoms:

Widespread rash, high body temperature and enlarged lymph nodes (DRESS or drug hypersensitivity syndrome).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	3 November 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	2 January 2025