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 the interaction with duloxetine, paediatric intoxication and Brugada syndrome, the PRAC considers a causal relationship between amitriptyline, amitriptyline / amitriptylinoxide, amitriptylinoxide and these risks is at least a reasonable possibility. The PRAC concluded that the product information of products containing amitriptyline, amitriptyline / amitriptylinoxide, amitriptylinoxide 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 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 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 amitriptyline, amitriptyline / amitriptylinoxide, amitriptylinoxide 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~~)

Interaction with duloxetine

Summary of Product Characteristics

Section 4.5

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CYP2D6 inhibitors: The CYP2D6 isozyme can be inhibited by a variety of drugs, e.g. neuroleptics, serotonin reuptake inhibitors, beta blockers, and antiarrhythmics. Examples of strong CYP2D6 inhibitors include bupropion, fluoxetine, paroxetine, and quinidine. These drugs may produce substantial decreases in TCA metabolism and marked increases in plasma concentrations. Consider to monitor TCA plasma levels, whenever a TCA is to be co-administered with another drug known to be a~~n~~ **strong** inhibitor of CYP2D6. Dose adjustment of amitriptyline may be necessary (see section 4.2). **Caution is advised in the case of co-administration of amitriptyline with duloxetine, a moderate CYP2D6 inhibitor.**

Package leaflet

- **Section 2**

Other medicines and amitriptyline

Some medicines may affect the action of other medicines and this can sometimes cause serious side effects. Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, such as:

• antidepressants (e.g. SSRIs (fluoxetine, paroxetine, fluvoxamine), **duloxetine,** and bupropion).

Paediatric intoxication

Summary of Product Characteristics

4.9 Section

Overdose with amitriptyline in children could have serious consequences. Children are especially susceptible to **coma,** cardiotoxicity, **respiratory depression,** seizures, hyponatraemia, **lethargy, sinus tachycardia, drowsiness, nausea, vomiting and hyperglycaemia.**

Package leaflet

Section 3

If you take more X than you should

Contact your doctor or nearest hospital casualty department immediately. Do this even if there are no signs of discomfort or poisoning. Take the container of this medicine with you if you go to a doctor or hospital.

Symptoms of overdose include:

- dilated pupils

- fast or irregular heartbeats
- difficulties passing water
- dry mouth and tongue
- intestinal blockage
- fits
- fever
- agitation
- confusion
- hallucinations
- uncontrolled movements
- low blood pressure, weak pulse, pallor
- difficulty breathing
- blue discolouration of the skin
- decreased heart rate
- drowsiness
- loss of consciousness
- coma
- various cardiac symptoms such as heart block, heart failure, hypotension, cardiogenic shock, metabolic acidosis, hypokalemia.

Overdose with amitriptyline in children could have serious consequences. Children are especially susceptible to coma, cardiac symptoms, difficulty in breathing, seizures, low blood sodium level, lethargy, drowsiness, nausea, vomiting and high blood sugar level.

Brugada syndrome

Summary of Product Characteristics

Section 4.9

Symptoms

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Cardiac symptoms: Arrhythmias (ventricular tachyarrhythmias, torsade de pointes, ventricular fibrillation). The ECG characteristically show prolonged PR interval, widening of the QRS-complex, QT prolongation, T-wave flattening or inversion, ST segment depression, and varying degrees of heart block progressing to cardiac arrest. Widening of the QRS-complex usually correlates well with the severity of the toxicity following acute overdoses. Heart failure, hypotension, cardiogenic shock. Metabolic acidosis, hypokalemia. **Post-marketing surveillance and literature reported cases of Brugada syndrome unmasking and Brugada ECG patterns (BEP) with amitriptyline overdose.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	5 November 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	4 January 2022