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 / perphenazine, the scientific conclusions are as follows:

In view of available data on the interaction with duloxetine, paediatric intoxication and Brugada syndrome, the PRAC considers (as in the case of the mono-component amitriptyline, amitriptyline / amitriptylinoxide, amitriptylinoxide) a causal relationship between amitriptyline / perphenazine and these risks is at least a reasonable possibility. The PRAC concluded that the product information of products containing amitriptyline / perphenazine 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 / perphenazine, the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing amitriptyline / perphenazine 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 / perphenazine 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

- **Adelco**

Summary of Product Characteristics

Section 4.5

Duloxetine: Potentially increased serotonergic activity when amitriptyline is co-administered with duloxetine.

Package leaflet

Section 2

Co-administration of amitriptyline with duloxetine can possibly increase the serotonergic activity

- **Mutabon**

Summary of Product Characteristics

Section 4.5

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Drugs metabolised by Cytochrome P450 2D6

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Moreover, some drugs inhibit the activity of this isoenzyme, thus placing intermediate metabolisers on the same plane as poorer metabolisers. Individuals displaying stability at a given dose of TCA may develop marked toxicity if subjected to concomitant therapy with one of these inhibitory drugs. Drugs that block cytochrome P450 2D6 comprise several that are not metabolised by the enzyme (quinidine, cimetidine), and many others that are substrates of P450 2D6 (numerous other antidepressants, phenothiazines, and the type 1C antiarrhythmic drugs propafenone and flecainide). All selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine, sertraline and paroxetine inhibit P450 2D6, **and moderate re-uptake inhibitors (SNRIS) such as duloxetine** although the magnitude of the inhibition produced may vary. The extent to which the interactions between TCAs ,SSRIs **and duloxetine (SNRI)** may create clinical issues depends on the level of inhibition and on the pharmacokinetics of the specific SSRI and **duloxetine** implicated. Nevertheless, care should be taken when administering a combination of TCA and any SSRI, **or duloxetine (SNRI)** even when switching from one class of drugs to another. It is particularly important to ensure an appropriate interval before commencing treatment with TCAs in a patient who has previously suspended fluoxetine administration: this is due to the long half-life of the active parent metabolite (a period of at least 5 weeks may be required).

Package leaflet

- **Section 2**

Other medicines and amitriptyline/perphenazine

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, propafenone and flecainide), **SNRI(duloxetine)**.

Paediatric intoxication

- **Adelco**

Summary of Product Characteristics

Section 4.9

Symptoms:

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

Overdose-treatment

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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.

- **Mutabon**

Summary of Product Characteristics

Section 4.9

Peadiatric population: Similar principles are adopted in the management of overdose in children and adults. The physician is strongly advised to contact the local poison control centre with regard to specific treatment in children. Although Mutabon Mite is not indicated for use in children, accidental ingestion may occur.

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.

Package leaflet

Section 3

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

- **Adelco**

Summary of Product Characteristics

Section 4.9

Symptoms:

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These events include extrapyramidal symptoms, progressive central nervous system suppression, from drowsiness to lethargy or coma with loss of reflexes, dyspnea, confusion, disturbances in concentration, transient visual hallucinations, agitation, hyperactive reflexes, discomfort, drowsiness, muscle stiffness, vomiting, hypothermia, hyperpyrexia, cardiovascular symptoms such as: arrhythmias (prolongation of QRS complex, ventricular tachyarrhythmias), electrocardiogram abnormalities, severe hypotension, heart failure, metabolic acidosis, hypokalemia, hyponatremia, convulsions/spasms, oculomotor paresis. **Post-marketing surveillance and literature reported cases of Brugada syndrome unmasking and Brugada ECG patterns (BEP) with amitriptyline overdose.**

- **Mutabon**

Summary of Product Characteristics

Section 4.9

Symptoms:

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The clinical manifestations of overdose of tricyclic antidepressants include: cardiac dysrhythmias, severe hypotension, convulsions and CNS depression, including coma. ECG alterations, particularly relating to QRS axis or depth, are clinically significant indicators of the toxicity of tricyclic antidepressants. **Post-marketing surveillance and literature reported cases of Brugada syndrome unmasking and Brugada ECG patterns (BEP) with amitriptyline overdose**. Other signs of overdose may include: confusion, concentration deficits, transitory visual hallucinations, dilatation of the pupils, agitation, hyperactive reflexes, stupor, somnolence, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed as adverse events.

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