

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:

Regarding hyponatraemia, in a recent retrospective study with 250 patients (66% in the paediatric group) by Paksu et al. (2014), the most common pathological clinical finding and laboratory abnormality were alteration of consciousness and hyponatremia. The authors concluded that amitriptyline poisoning may be associated with life-threatening complications, especially in paediatric age group and in patients with hyponatremia in which group the incidence was higher. Based on this review, the role of amitriptyline in the reported cases, the assessment and the proposed wording provided by some of the MAHs, the PRAC considers necessary an update in section 4.9 of the SmPC to add hyponatraemia in cardiac symptoms and in the section with information on children overdose.

Hallucinations are a known adverse reaction with amitriptyline, and they are listed in the SmPC. However, hallucinations are only listed as 'connected to schizophrenic patients'. Based on the data provided in the current procedure, it seems there is not a consistent pattern of reported hallucinations to be connected only with schizophrenic patients. In addition, all types of hallucinations, visual, auditory and mixed type are reported. Therefore, the PI should be updated to include hallucinations but not only connected to schizophrenic patients.

The findings of the study in the article by Stefan Unterecker et al. suggest a clinically highly relevant interaction between amitriptyline/nortriptyline and valproic acid, leading to an increase of amitriptyline/nortriptyline serum level. In addition, this interaction is already mentioned in the Stockley's Drug Interactions and the PI of some valproic acid containing medicinal products (e.g. Depakine). Based on the above, the PI of amitriptyline contacting medicinal products should be updated to include the interaction between amitriptyline with valproic acid.

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~~)

Summary of Product Characteristics

- Section 4.5

Amitriptyline plasma concentration can be increased by sodium valproate and valpromide. Clinical monitoring is therefore recommended.

- Section 4.8

The following adverse reaction under the SOC 'Psychiatric disorders' with a frequency rare, should be amended as follows:

hallucination (~~in schizophrenic patients~~)

- Section 4.9

Cardiac Symptoms:

... Metabolic acidosis, hypokalaemia, **hyponatraemia**

And in the part about overdose in children:

Children are especially susceptible to cardiotoxicity, ~~and~~ seizures and **hyponatraemia**.

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:

Valproic acid

- Section 4

Rare: may affect up to 1 in 1,000 people

- delirium (especially in elderly patients), hallucinations (~~especially in patients with schizophrenia~~),

Annex III

Timetable for the implementation of this position

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Adoption of CMDh position:	September 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	03 November 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	02 January 2019