

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 nortriptyline, the scientific conclusions are as follows:

In view of available data on Brugada syndrome from the literature and spontaneous reports including close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC LMS considers a causal relationship between nortriptyline and Brugada syndrome is at least a reasonable possibility. The PRAC LMS concluded that the product information of products containing nortriptyline should be amended accordingly.

In view of available data on hyponatraemia from the literature and in view of a plausible mechanism of action, the PRAC LMS considers a causal relationship between nortriptyline and hyponatraemia is at least a reasonable possibility. The PRAC LMS concluded that the product information of products containing nortriptyline 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 nortriptyline the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing nortriptyline 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~~)

Summary of Product Characteristics

Section 4.4

A warning should be added as follows:

Cardiac arrhythmias are likely to occur with high dosage. They may also occur in patients with preexisting heart disease taking normal dosage.

Unmasking of Brugada syndrome has been reported in patients treated with nortriptyline. Brugada syndrome is a rare hereditary disease of the cardiac sodium channel with characteristic ECG changes (ST segment elevation and T wave abnormalities in the right precordial leads), which may lead to cardiac arrest and/or sudden death. Nortriptyline should generally be avoided in patients with Brugada syndrome or those suspected of having Brugada syndrome. Caution is advised in patient with risk factors such as a family history of cardiac arrest or sudden death (see sections 4.8 and 4.9).

- Section 4.8

The following adverse reaction should be added under the SOC "Cardiac disorders" with a frequency unknown:

Brugada Syndrome (unmasking) (frequency unknown)

The following adverse reaction should be added under the SOC "Metabolism and nutrition disorders" with a frequency unknown:

Hyponatraemia

- Section 4.9

The recommendations for symptoms of overdose should be added as follows:

Brugada syndrome (unmasking) and Brugada ECG pattern (BEP) have been reported in post-marketing surveillance in association with nortriptyline overdose.

Package Leaflet

Section 2. What you need to know before you take X

Talk to your doctor before taking X

- if you have a cardiac condition called Brugada syndrome

4. Possible side effect

Frequency unknown:

Brugada Syndrome (unmasking) (symptoms may include very fast heartbeat, dizziness, fainting, seizures). Tell your doctor straight away if you get these symptoms.

Frequency unknown:

Low sodium concentration in the blood

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	<i>December 2023</i> CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	<i>28 January 2024</i>
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	<i>28 March 2024</i>