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 donepezil, the scientific conclusions are as follows:

In view of several literature reports (Segrec et al. 2015, six case reports published by Triquet et al. 2017, Lo Coco and Cannizzaro 2010, Chemali 2003), in which the temporal relationship between the initiation of donepezil and the onset of inappropriate sexual behaviours (ISB), the prompt resolution of symptoms following discontinuation of donepezil, and the recurrence shortly after re- initiation in some cases, strongly supports a relationship between ISBs and donepezil, the PRAC recommends to add the term libido increased, hypersexuality to the product information.

Based on the available data including literature articles and relevant post-marketing cases showing improvement or cessation of sleep-related ADRs after switching from evening to morning administration, the PRAC recommends including an advice to consider switch to morning administration if sleep-related ADRs occur.

In view of the available data, including post-marketing reports and several literature reports suggesting a causal relationship between donepezil and pleurothotonus, including cases with positive de-challenge and two literature cases with positive de- and re-challenge, and given the plausible mechanisms of dopaminergic-cholinergic imbalance, the PRAC recommends to add Pisa syndrome / pleurothotonus to the product information with the frequency 'not known'.

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 donepezil the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing donepezil 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 donepezil 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

- SmPC section 4.2

Method of administration

<Product name> should be taken orally, in the evening, just prior to retiring.

In case of sleep disturbances including abnormal dreams, nightmares or insomnia (see section 4.8) intake of <product name> in the morning may be considered.

- SmPC section 4.8

The following adverse reaction should be added with the frequency "not known" under the SOC Psychiatric disorders:

Not known: **libido increased, hypersexuality**

The following adverse reaction should be added with the frequency "not known" under the SOC Nervous system disorders:

Not known: **Pleurothotonus (Pisa syndrome)**

Package Leaflet

- PL section 3:

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

*Note: The following sentence should be added at **an** appropriate place in section 3 of PL (preferably directly below the paragraph which contains the **first** instructions for evening intake shortly before going to bed):*

If you experience abnormal dreams, nightmares or difficulty in sleeping (see section 4) your doctor may advise you to take <product name> in the morning.

- PL section 4:

Not known (frequency cannot be estimated from the available data): **libido increased, hypersexuality.**

Not known (frequency cannot be estimated from the available data): **Pisa syndrome (a condition involving involuntary muscle contraction with abnormal bending of the body and head to one side)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	4 September 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	3 November 2022