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 clomipramine, the scientific conclusions are as follows:

In view of available data on 'cardiomyopathy' and 'cardiac failure' from spontaneous reports including in four cases a positive de-challenge, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between clomipramine and 'cardiomyopathy' and 'cardiac failure' is at least a reasonable possibility. The PRAC concluded that the product information of products containing clomipramine should be amended accordingly.

In view of available data on 'cardiac septal defects' from the literature and spontaneous reports including in five cases a close temporal relationship and in view of a plausible mechanism of action, the PRAC considers a causal relationship between clomipramine and 'cardiac septal defects' is at least a reasonable possibility. The PRAC concluded that the product information of products containing clomipramine should be amended accordingly.

In view of available data on 'status cataplecticus' from literature, including in four cases a close temporal relationship and in two cases a positive de-challenge, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between clomipramine and 'status cataplecticus' is at least a reasonable possibility. The PRAC concluded that the product information of products containing clomipramine 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 clomipramine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing clomipramine 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 amended as follows:

Treatment Discontinuation

Patients with cataplexy may experience worsening of cataplexy symptoms including status cataplecticus upon abrupt withdrawal.

- Section 4.6

New information with regards to the risk(s) of the product when used during pregnancy should be added as follows:

Data from Swedish health registries with 1,029 women exposed to clomipramine in the first trimester do not suggest an increased risk of overall congenital anomalies in the offspring. However, the risk for any cardiac defect was increased (risk of 2/100 compared to 1/100 in the general population). The strongest association was found for ventricular or atrial septal defects.

- Section 4.8

The following adverse reaction(s) should be added under the SOC 'Cardiac disorders' with a frequency 'not known':

cardiomyopathy, cardiac failure

Package Leaflet

2. What you need to know before you take <product name>

Pregnancy and breast-feeding

Available data do not suggest an increased risk of overall birth defects. However, some data from health registries suggest an increased risk of heart malformations when clomipramine was used during the first three months of pregnancy (2 cases in 100 pregnancies) compared to the general population (1 case in 100 pregnancies).

3. How to take <product name>

If you stop taking <product name>

If you suffer from cataplexy, your symptoms may get worse when you stop the medicine suddenly.

Section 4. Possible side effects:

Not known: frequency cannot be estimated from available data:

- Damage to the heart muscle (cardiomyopathy)
- Heart failure

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	13 November 2025
Transmission to National Competent Authorities of the translations of the annexes to the position:	28 December 2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 February 2026