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 for the non-interventional imposed PASS final report for the medicinal product(s) containing the active substance lisdexamfetamine dimesylate (LDX) and concerned by the PASS final report, the scientific conclusions are as follows:

PASS SPD489-825, a non-interventional, imposed, population-based cohort study was conducted using Danish and Swedish National Registers. The study compared a cohort of adult patients who were new users of LDX with a cohort of patients with remote use of other ADHD medications, matched on age, sex, region, and cohort entry date.

While the overall study results do not provide evidence for an increased cardiovascular risk these overall estimates are derived from a study population where most patients had a short-term exposure of LDX. In the analysis of long-term use of LDX there was a higher estimated risk of MACE among LDX users compared to what was seen in the overall study population. The focus on an increased relative risk of MACE above the prespecified threshold of 3.00 to be clinically relevant is not fully appropriate. There is some evidence of increased cardiovascular risk related to long-term exposure but despite the large study population the estimation of risk associated with true long-term LDX exposure remains uncertain in this study. The results do not, however, warrant any further regulatory action. The extensive contraindications and warnings currently in place concerning cardiovascular risk remain relevant.

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 the results of the study for the medicinal product(s) containing the active substance lisdexamfetamine dimesylate and concerned by the PASS final report, the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) mentioned above is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of the products concerned by this PASS final report should be varied.

Annex II

Conditions to the Marketing Authorisation(s)

Changes to be made to the conditions of the marketing authorisation(s) of medicinal product(s) containing the active substance lisdexamfetamine dimesylate concerned by the non-interventional imposed PASS final report

The marketing authorisation holder(s) shall remove the following condition(s) (new text **<u>underlined and in bold</u>,** deleted text ~~strike through~~):

~~SPD489-825: Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Lisdexamfetamine and Remote Adult Users of Other ADHD Treatments~~

~~End of data collection: by 31 December 2020~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of the position

Adoption of CMDh position:	September 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	1 November 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 December 2021