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 dexamfetamine and concerned by the PASS final report , the scientific conclusions are as follows:

This was a 5-year retrospective (open) cohort study of new users, gathered data from three healthcare databases (in UK, US and Germany), compared the relative risk between dexamfetamine and other stimulants, with the aim to assess incidence proportion and incidence rate for cardiovascular, psychiatric, growth and sexual maturity-related AE in children with ADHD diagnosis, treated with dexamfetamine, methylphenidate, lisdexamfetamine, or dexmethylphenidate (in US only) and compare the risk of the AEs above mentioned between these medicines.

Dexamfetamine had a significantly higher unadjusted incidence proportion of psychiatric disorders and the composite outcome compared with methylphenidate and lisdexamfetamine. It also showed higher unadjusted incidence rate of psychiatric disorders than methylphenidate and lisdexamfetamine and higher unadjusted incidence rate for the composite outcome than methylphenidate. When multivariable ajusted models and propensity-score matching were considered, dexamfetamine was associated with increased odds for growth impairment (1.2) and increased odds for the composite endpoint (1.1) when compared with methylphenidate. The study is unable to quantify absolute differences in growth, only to compare the proportion of patients diagnosed with this problem (yes or no) across the studied medicines. However, hazard ratios calculated using multivariable adjusted models and propensity-score matched models showed no differences in any of the adverse events of interest when comparing dexamfetamine to the other medicines in the study.

Overall, the study indicates that dexamfetamine could be as safe as other stimulants prescribed for attention deficit hyperactivity disorder regarding cardiovascular, phychiatric, or sexual maturity disorders. However, there could be a small, but clinically significant higher incidence of growth impairment for dexamfetamine users when compared with methylphenidate. The study does not allow for definitive conclusions as the target sample size for dexamfetamine users was not available in the databases and estimates for this medicine are associated with wide confidence intervals.

There was strong heterogeneity between databases (very large differences in incidence of adverse events were found between the European databases and the United States database), with patients from the United States having the highest incidence of adverse events and the narrowest confidence intervals for estimations. Hence, the study focuses mainly on the results originating from the United States. It is likely that these differences between databases result mainly from their ability to capture data and not from different effects of these medicines in the United States or European populations.

Over the course of the procedure the MAH provided clarifications, notably differences between databases were justified as being caused by how data are captured and, given that dexamfetamine is indicated only when response to previous methylphenidate treatment is considered clinically inadequate, and that the risks identified by the PASS are already described in the current SmPC, the benefit-risk balance remains unchanged and addition of wording in section 4.8 was not considered necessary. Safety signals regarding growth impairment and sexual maturation disorders might merit additional investigation but this could be further followed in the PSURs. No further measures seem really needed at this stage.

Therefore, the MAH should submit an updated RMP at the next regulatory opportunity in order to address that this marketing authorization condition has been fulfilled.

As a result of the fulfilment of the study, the products should be removed from the list of medicines under additional monitoring.

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 dexamfetamine 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 dexamfetamine 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~~)

~~Post-authorisation Safety Study to Evaluate the Long-termSafety of Dexamfetamine~~

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