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 lisdexamphetamine, the scientific conclusions are as follows:

The PRAC considered currently available information with regards to the risks of lisdexamphetamine, amphetamine and dextroamphetamine exposure during pregnancy:

- The PRAC reviewed the Huybrechts et al. 2018 study. It is generally a well conducted study, where association between methylphenidate and amphetamine/-dextroamphetamine use in pregnancy, respectively and risk of congenital malformations were studied in a large cohort. The amount of first trimester exposure to amphetamine/dextroamphetamine is large; corresponding to about 5570 pregnancies. There is no indication of an increased occurrence of congenital malformations in this dataset (any congenital malformation, fully adjusted, 1.05 [0.93-1.19] 95% CI).
- Another cohort study (Cohen et al. 2017) was also considered by the PRAC. This study involved approximately 3100 pregnancies exposed to amphetamine/dextroamphetamine. It identified an increased risk of pre-eclampsia (adjusted RR 1.33 (95% CI 1.12-1.58)) and suggested an increased risk of preterm birth in association with exposure to amphetamine-dextroamphetamine in the first 20 weeks of pregnancy. Increased occurrence of preterm birth is also known from women being dependant on amphetamine and using it during pregnancy.
- Finally, the PRAC considered the primary pharmacological properties of lisdexamphetamine being a stimulant for which withdrawal symptoms may occur at abrupt discontinuation, and that withdrawal symptoms have been reported with lisdexamphetamine use (See Section 4.4 of the SmPC). Withdrawal symptoms are also a potential risk in the RMP. Furthermore, the PRAC noted experience from women being dependent on amphetamine and using it during pregnancy, where their newborns may develop withdrawal symptoms. The PRAC also took into account two case reports of withdrawal syndrome in newborns of women treated with lisdexamphetamine during pregnancy, from the PSUR period.

Based on the above, the PRAC considers that updates to the section 4.6 of the SmPC and 2 of the PL are warranted to describe the current information from use of lisdexamphetamine, amphetamine and dextroamphetamine during pregnancy.

Based on the information received during the review period, it is concluded that the benefit-risk balance of lisdexamphetamine in the licensed indication in the treatment of ADHD remains unchanged.

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

Section 4.6

~~"There are no adequate and well controlled studies of Tradename in pregnant women."~~

Data from a cohort study of in total approximately 5570 pregnancies exposed to amphetamine in the first trimester do not suggest an increased risk of congenital malformation. Data from another cohort study in approximately 3100 pregnancies exposed to amphetamine during the first 20 weeks of pregnancy, suggest an increased risk of preeclampsia, and preterm birth. Newborns exposed to amphetamine during pregnancy may experience withdrawal symptoms.

Package Leaflet

- Section 2

2. What you need to know before you take [TRADENAME]

Pregnancy, breast-feeding and fertility

~~It is not known if Tradename will affect an unborn baby.~~

Available data from the use of [Tradename] during the first three months of pregnancy do not indicate increased risk of congenital malformation in the child, but may increase the risk for pre-eclampsia (a condition usually occurring after 20 weeks of pregnancy characterized by high blood pressure and protein in the urine) and preterm birth. Newborns exposed to amphetamine during pregnancy may experience withdrawal symptoms (trembling, irritability, tight muscle tone).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	01 December 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 January 2020