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 rizatriptan, the scientific conclusions are as follows:

The available evidence from more than 700 prospective pregnancies included in pharmaco-epidemiological studies, 34 spontaneous post-marketing cases of interest with expected first trimester exposure, and animal studies justifies an update of the information in SmPC section 4.6. Data from different sources up to now do not indicate an increased teratogenic risk when rizatriptan is used in the first trimester of pregnancy. Regarding the second and third trimester of pregnancy, there is limited information available. It should be taking into account, however, that the condition of migraine also poses a risk on the unborn child in particular during these trimesters. The LMS, therefore, recommends an updated advice for use of rizatriptan during pregnancy.

It is further recommended by the LMS to reduce the waiting time to feed a child when women are breastfeeding while using rizatriptan. Data in breast-feeding women (Amundsen et al. 2021) showed that rizatriptan is excreted in human milk, but in a low concentration. A RID was calculated based on the average concentration of triptan in milk over 24 hours. This RID for rizatriptan was 0.9% (range = 0.3-1.4%) which translated to an absolute infant dose of 0.4-3.2 μg/kg. Rizatriptan was not detected in any of the 24 hr samples. The RID for rizatriptan based on Cmax in milk (worst case scenario) was 5.6% (range = 1.7-9.7%). Based on the short half-live (2 to 3 hours) of rizatriptan and the low concentration of rizatriptan that is excreted in human milk, the period to wait with breastfeeding after administration of rizatriptan can be reduced from 24 hours to 12 hours. This clinical finding should replace the non-clinical findings that are currently included in SmPC section 4.6.

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 rizatriptan the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing rizatriptan 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 4.6

SmPC

<….>

Pregnancy

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative toxicity following first trimester exposure. Animal studies do not indicate reproductive toxicity (see section 5.3).

There is limited data in relation to use of rizatriptan in the second and third trimester of pregnancy. Use of rizatriptan may be considered during pregnancy, if clinically necessary.

~~The safety of rizatriptan for use in human pregnancy has not been established. Animal studies do not indicate harmful effects at dose levels that exceed therapeutic dose levels with respect to the development of the embryo or foetus, or the course of gestation, parturition and postnatal development.~~

~~Because animal reproductive and developmental studies are not always predictive of human response, <product name> should be used during pregnancy only if clearly needed.~~

Breastfeeding

~~Studies in rats indicated very high milk transfer of rizatriptan occurred. Transient, very slight decreases in preweaning pup body weights were observed only when the mother's systemic exposure was well in excess of the maximum exposure level for humans. No data exist in humans.~~

Rizatriptan is excreted in low concentration in human milk with an average relative infant dose less than < 1% (less than 6% in worst case scenario based on Cmax in breastmilk). ~~Therefore,~~ Caution should be exercised when administering rizatriptan to women who are breast-feeding. Infant exposure ~~should~~ **may** be minimised by avoiding breast-feeding for **12** ~~24~~ hours after administration of rizatriptan.

Package Leaflet

- Section 2

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Available data on the safety of rizatriptan when used during the first 3 months of pregnancy do not suggest an increased risk of birth defects. It is not known whether <product name> is harmful to an unborn baby when taken by a pregnant woman **after the first 3 months of pregnancy.**

If you are breastfeeding, you may postpone breastfeeding for 12 hours after treatment to avoid exposure in your baby.

~~Breastfeeding should be avoided for 24 hours after treatment.~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	February CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	7 April 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	6 June 2024