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 misoprostol (gynaecological indication - termination of pregnancy), the scientific conclusions are as follows:

Follow-up visits after medical termination of pregnancy with misoprostol are considered obligatory due to the risk of foetal malformations in case of method failure and ongoing pregnancy. It is important that both the summary of product characteristics (SmPC) and product leaflet (PL) contain sufficient warnings about the need for such follow-up visits.

It is established that exposure to misoprostol during pregnancy can cause a range of foetal malformations. In the section 4.6 of the current SmPC only Moebius syndrome (facial paralysis) and amniotic band syndrome (various limb defects) are mentioned. During the interval Auffret et al. 2016 published the largest prospective cohort study about risk of malformations in foetuses exposed to misoprostol during the first trimester of pregnancy. Out of 183 pregnancies exposed to misoprostol four major malformations were identified which were related to central nervous system (hydrocephalus, encephalocele, cerebellar hypoplasia and pituitary stem interruption syndrome). Cases of central nervous system malformations after misoprostol exposure have also been reported in the past in studies by Vauzelle et al., 2013, Barbero et al., 2011, Dal Pizzol et al., 2008 and Orioli et al., 2000. The pattern of malformations described in section 4.6 of the SmPC should be updated in accordance with this knowledge.

With regards the frequency of the malformations, the study published by Auffret et al, 2016 confirms the results of previous prospective epidemiological studies with a rate of malformations in the same order of magnitude (5.5% in Auffret et al. 2016; 4% in Vauzelle et al., 2013; 6.5% in Barbero et al., 2011; 4.2% in Dal Pizzol et al., 2008). A meta-analysis of the combined studies revealed an odds ratio (OR) of foetal malformations of 2.7 (95% confidence interval: 1.54-4.74).

The term “Foetal malformations” is considered more appropriate than “Birth defects. “Foetal malformations” covers diagnosis both in utero as well as post-partum, whereas “Birth defects” is solely a post-partum diagnosis.

Moreover, one MS proposed to add the addition of “hypomimia, troubles of sucking and deglutition and eye movements” which are neonatal consequences described with the Moebius syndrome. PRAC considers that this is important information health care professionals and patients and endorses the MAH proposal to include this information in section 4.6 of the SmPC.

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 misoprostol (gynaecological indication - termination of pregnancy) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing misoprostol (gynaecological indication - termination of pregnancy) 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 misoprostol (gynaecological indication - termination of pregnancy) 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 4.4

  Exposure of the foetus to misoprostol or mifeprostone increases the risk of developing Moebius syndrome and/or an amniotic band syndrome **and/or central nervous system anomalies (see section 4.6)**. A second termination of pregnancy procedure shall be considered. In case of continuation of the pregnancy close monitoring by ultrasound scan must be performed in specialised centres.

- Section 4.6

  Failure of pregnancy termination (continuing pregnancy) ~~Use in pregnancy~~ has been associated with **a 3-fold increased risk of** birth defects/malformations for ongoing pregnancies exposed to mifepristone and misoprostol or misoprostol alone, **compared to control group (about 2%)**. **In particular, p**~~P~~renatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis **leading to hypomimia, troubles of sucking and deglutition and eye movements**, with or without limb defects) and with amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, olygodactyly, cleft palate inter alia)**, and central nervous system anomalies (cerebral and cranial anomalies such as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects).**

  Women considering medical termination of pregnancy should be precisely counselled on the risks to their foetus if an abortion failure occurs and a second termination of pregnancy procedure is not desirable.

  (…)

  Should the patient wish to continue with her pregnancy, a careful ultrasound scan monitoring of the pregnancy, with a special attention to the limbs **and head**, must be established in a specialised centre.

- Section 4.8

  The frequency of the adverse reaction of birth defects should be revised to **Common**, and the Preferred Term (PT) should be changed to "**Foetal malformations**".

Package Leaflet

- Section 2. What you need to know before you take X

  Warnings and precautions

  Health care professionals should ensure that due to the risk of the failure of the method and the birth defects observed in these ongoing pregnancies, patients are being informed about the risk of teratogenicity and that a follow-up visit must be scheduled in order to check that the expulsion is completed (see section Pregnancy, breast-feeding and fertility).

Pregnancy, breast-feeding and fertility

Failure of pregnancy termination (continuing pregnancy) after taking X after the first medicine (mifepristone) has been associated with **a 3-fold increased risk of** birth defects, **in particular facial paralysis, head and limb malformations.**

(…)

If you decide to continue with the pregnancy, careful pre-natal monitoring and repeated ultrasound examinations, with a special attention to the limbs **and head**, in a specialised clinic must be carried out.

- Section 4. Possible side effects

Other side effects:

Common (may affect up to 1 in 10 people):

Birth defects (foetal malformations)

Annex III

Timetable for the implementation of this position>

Timetable for the implementation of this position

Adoption of CMDh position:	January 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10 March 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	9 May 2018