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 mifepristone / misoprostol, the scientific conclusions are as follows:

The cumulative review of uterine rupture including literature search, identified nine cases, two cases were received with Combipack of Mifepristone and Misoprostol and remaining seven cases were received with misoprostol only. 14 publications were considered to be relevant regarding these medicinal products and uterus rupture. These publications showed an increased risk of uterine rupture for both the combination of mifepristone/misoprostol as well as misoprostol alone for the indications termination of pregnancy beyond 63 days or labour induction. Despite the occurrence of uterine rupture with off-label use, it seems appropriate to report this adverse drug reaction in the summary of product characteristics (SmPC). Moreover, similar marketing authorisations of combinations of mifepristone/misoprostol for the same indication include the adverse drug reaction "uterine rupture" in section 4.8 of the SmPC with frequency "rare". In this light, PRAC recommends to include "uterine rupture" in section 4.8 under the system organ class (SOC) "Injury, poisoning and procedural complications" with frequency "rare", but highlight with an asterisk the following explanatory text:

"Uterine rupture has been uncommonly reported after prostaglandin intake for induction of termination of second trimester pregnancy or labour induction for foetal death in utero in the third trimester. Uterine ruptures occurred particularly in multiparous women or in women with a caesarean section scar."

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 mifepristone / misoprostol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing mifepristone / misoprostol 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 mifepristone / misoprostol 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 4.8

"**Uterine rupture ***" should be added under the SOC Injury, poisoning and procedural complications with a frequency **"rare"**

"* Uterine rupture has been uncommonly reported after prostaglandin intake for induction of termination of second trimester pregnancy or labour induction for foetal death in utero in the third trimester. Uterine ruptures occurred particularly in multiparous women or in women with a caesarean section scar.'

Package Leaflet

Section 4

Tearing of the womb (uterine rupture)

'Tearing of the womb after administration of prostaglandins in the second or third trimester of pregnancy, mainly in women with previous deliveries of a child or with a scar of a caesarian section.

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