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 the medicinal products containing misoprostol (gynaecological indication - labour induction) 200 microgram vaginal insert formulation, the scientific conclusions are as follows:

The PRAC noted that in the Miso-Obs-303 study, the adverse drug reaction ‘uterine tachysystole’ did not subside with the use of tocolysis in 5 (0.7 %) of the subjects. From this information, it can be settled that excessive uterine tachysystole that may not respond to tocolytic treatment is in fact causally associated with the use of Misodel, even under circumstances of correct use according to the summary of product characteristics (SmPC). A few of the post-marketing cases are in further support of this observation. The PRAC considers that this is a new aspect of a known adverse reaction, and recommends to reinforce the existing warning in section 4.4 of the SmPC about the risk of excessive uterine tachysystole which may not respond to tocolytic treatment, even when Misodel is used correctly and in accordance with the SmPC.

Therefore, in view of the data presented in the reviewed PSUR of Misodel 200 mcg vaginal insert, the PRAC considered that changes to the product information of medicinal products containing misoprostol 200 mcg vaginal insert for indication labour induction were warranted.

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 - labour induction) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing misoprostol (gynaecological indication - labour induction) as a 200 mcg vaginal insert formulation 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 - labour induction) as a 200 mcg vaginal insert formulation are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

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 **<u>underlined and in bold</u>**, deleted text ~~strike-through~~)

Summary of Product Characteristics

- Section 4.4

A warning should be revised as follows:

~~Misodel can cause excessive uterine stimulation if left in place after onset of active labour (see Section 4.9).~~

~~If uterine contractions are prolonged or excessive, or there is a clinical concern for the mother or baby, remove the vaginal delivery system. If excessive uterine contractions continue after drug removal, tocolytic treatments should be considered.~~

<u>Misodel can cause excessive uterine tachysystole that may not respond to tocolytic treatment. Close monitoring is needed in order to ensure removal of the vaginal delivery system immediately at onset of labour or if uterine contractions are prolonged or excessive or if there is a clinical concern for the mother or baby.</u>

Package Leaflet

2. What you need to know before you are given Misodel

Warnings and precautions

~~Misodel can cause strong womb stimulation if left in place after onset of labour (see "If you use more Misdodel than you should" below).~~

~~In case the womb contractions are prolonged or strong or your doctor or nurse is concerned for you or your baby, Misodel will be removed. If the womb contractions continue after removal of Misodel, tocolytic treatment may be given which will slow down your contractions.~~

<u>Misodel can cause strong and prolonged womb contractions. The use of Misodel is therefore closely monitored to ensure that Misodel is removed as early as possible. Sometimes it is necessary to add another medication (tocolytic treatment), which in most cases will resolve the contractions.</u>

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 March 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 May 2017