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 (gastrointestinal indication), the scientific conclusions are as follows:
Teratogenicity is an important risk related to off-label-use of Cytotec. Since off-label use of Cytotec is highly prevalent, appropriate warnings in the SmPC are important to enable healthcare professionals to make informed decisions not only in order to avoid exposure during pregnancy, but also in cases where misoprostol exposure has happened during pregnancy. Therefore, as a risk minimisation effort, and in line with the outcome of previously finalised procedure (PSUSA/00010354/201705) for misoprostol-containing products indicated for termination of pregnancy, a revision of the SmPC to add information about the risk of teratogenicity in relation to use during pregnancy in accordance with current knowledge is recommended. As primary grounds for the update lies the scientific publication by Auffret et al. 2016, which supported the effect of misoprostol exposure during early pregnancies on cerebral anomalies of the foetuses, and which confirmed the results of previous prospective epidemiological studies by finding a rate of foetal malformations in the same order of magnitude. Several cases of uterine rupture have been reported during this PSUSA, all occurred with off-label use. Therefore, the PRAC recommends the update the frequency of the adverse drug reaction (ADR) from "unknown" to "rare" and also the addition of a description of the ADR.

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 (gastrointestinal indication) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing misoprostol (gastrointestinal indication) 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 (gastrointestinal indication) 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 **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.3

A contraindication should be added as follows:

Misoprostol is contraindicated:

- In women of childbearing potential who are not using effective contraception (see sections 4.4, 4.6 and 4.8)

- In women who are pregnant, or in whom pregnancy has not been excluded, or who are planning a pregnancy as misoprostol increases uterine tone and contractions in pregnancy which may cause partial or complete expulsion of the products of conception (see sections 4.4, 4.6 and 4.8). Use in pregnancy has been associated with birth defects.

- Section 4.6

A warning should be revised as follows:

Women of childbearing potential

Women of childbearing potential must be informed about the risk of teratogenicity prior to treatment with Cytotec. Treatment must not be initiated until pregnancy is excluded, and women should be fully counselled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, treatment must be immediately discontinued (see sections 4.3 and 4.4).

Pregnancy

Misoprostol is contraindicated in women who are pregnant because it induces uterine contractions and is associated with abortion, premature birth, foetal death and ~~birth defects~~ **foetal malformations**. ~~First trimester exposure to misoprostol is associated with a significantly increased risk of two birth defects: Möbius sequence (i.e. palsies of cranial nerves VI and VII) and terminal transverse limb defects.~~ **Approximately a 3-fold increased risk of malformations was reported in pregnancies exposed to misoprostol during the first trimester, compared to a control group incidence of 2%. In particular, prenatal 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); amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, olygodactyly, cleft palate inter alia) and central nervous system anomalies (cerebral and cranial anomalies as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects).** Other defects including arthrogryposis have been observed.

Consequently:

- Women should be informed of the risk of teratogenicity.
- Should the patient wish to continue with her pregnancy after exposure of misoprostol in utero, a careful ultrasound scan monitoring of the pregnancy, with a special attention to the limbs and head must be carried out.
(…)

- Section 4.8

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

The frequency of the adverse reaction of uterine rupture should be changed to **Rare**. Moreover, a reference (**) should be added, together with a description below the Table:

****Uterine rupture has been uncommonly reported after prostaglandin intake during the second or third trimester of pregnancy. Uterine ruptures occurred particularly in multiparous women or in women with a caesarean section scar.**

Package leaflet
2. Before you take Cytotec

Do not take Cytotec if you:

• **are a woman of childbearing age and you are not using an effective contraceptive method to avoid becoming pregnant** (see Section 'Pregnancy' for further information).

• are pregnant or trying to become pregnant **or do not have a negative pregnancy test** because it may cause a miscarriage (see Section 'Pregnancy' for further information).

Warnings and precautions:

Talk to your doctor or pharmacist before taking Cytotec, if you

- **are pregnant or plan to become pregnant (see subsection "pregnancy" below). Due to the risk for the foetus, your treatment with X must be discontinued immediately.**
- **are a woman of childbearing age (see subsection "pregnancy" below). Due to the risk for the foetus, it is important to use effective contraception while you are taking X.**
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Pregnancy and lactation

If you are pregnant or breastfeeding or suspects pregnancy or planning to become pregnant, you must seek advice from your doctor or pharmacist before starting the treatment.

regnancy:

Do not take Cytotec if you are pregnant or plan to become pregnant. Your doctor will make you aware of the risks if you do become pregnant as Cytotec may cause a miscarriage, premature birth or birth defects. Pregnancies exposed to misoprostol during the first trimester have been associated with approximately a 3-fold increased risk of birth defects, in particular facial paralysis, limbs defects, cerebral and cranial anomalies. If you are exposed to Cytotec during pregnancy, talk with your doctor. 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 must be carried out.

4. Possible side effects

Serious side effects:

Common:

Birth defects (foetal malformations). If you become pregnant during treatment, stop taking Cytotec immediately and seek medical advice.

Rare:

Tearing of the womb (uterine rupture) 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 caesarean section. Seek urgent medical attention.

Not known:

~~Birth defects~~

~~Tearing of the tissues in the womb~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	February 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	07 April 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	06 June 2018