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 diclofenac / misoprostol, the scientific conclusions are as follows:

Based on a study by Auffret et al. 2016 on the effect of misoprostol exposure during early pregnancies on cerebral anomalies that showed a rate of foetal malformations in the same order of magnitude of previous prospective epidemiological studies and in view of the data presented in the reviewed PSUR(s) for diclofenac / misoprostol, the PRAC considered that a revision of the summary of product characteristics (SmPC) to reflect its teratogenicity is warranted. In addition, the PRAC also considered it important that the possible risks with exposure to non-steroidal anti-inflammatory drugs like diclofenac in pregnant women, in line with the wording provided in the SmPCs of acetylsalicylic acid and non-steroidal anti-inflammatory drugs with regard to use during pregnancy and risk of miscarriage and congenital malformations as agreed by the PhVWP in April 2004 – (Ref: EMEA/12148/04/Final), should be reflected in the product information.

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 diclofenac / misoprostol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing diclofenac / 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 diclofenac / 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 4.3

A contraindication should be added as follows:

[XX] is contraindicated in:

[…]

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

[…]

- Section 4.4

A warning should be revised as follows:

~~Use in pre-menopausal~~ **In** women **of childbearing potential** (see also section 4.3) **[product name]** ~~should~~ **must** not be used ~~in pre-menopausal~~ ~~women~~ unless they use effective contraception and have been advised of the risks of taking the product if pregnant (see section 4.6).

The label will state: 'Not for use in ~~pre-menopausal~~ women **of childbearing potential** unless using effective contraception'.

- Section 4.6

Pregnancy

[XX] is contraindicated in pregnant women and in women planning a pregnancy**.**

Misoprostol:

~~because m~~**M**isoprostol induces uterine contractions and is associated with abortion, premature birth, ~~and~~ foetal death **and foetal malformations**. ~~Use of misoprostol has been associated with birth 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 suckling 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 special attention to the limbs and head must be carried out.

Diclofenac:
~~Also diclofenac may cause premature closure of the ductus arteriosus.~~
Inhibition of prostaglandin synthesis might adversely affect pregnancy **and/or the embryo/foetal development**. Data from epidemiological studies suggest an increased risk of ~~spontaneous abortion~~ **miscarriage and of cardiac malformation and gastroschisis** after use of prostaglandin synthesis inhibitors in early pregnancy. **The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy.** In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss **and embryo-foetal lethality**. **In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.**

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- **cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);**
- **renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;**

the mother and the neonate, at the end of pregnancy, to:

- **possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.**
- **inhibition of uterine contractions resulting in delayed or prolonged labour.**

Breastfeeding
[…]

Fertility
[…]

Women of childbearing potential
Women of childbearing potential ~~should not~~ **must** be **informed about the risk of teratogenicity prior to treatment with** ~~started on~~ diclofenac-misoprostol**. 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, ~~use of the product should~~ **treatment must** be **immediately** discontinued **(see section 4.3, 4.4 and 4.8).**

- Section 4.8

The frequency of the adverse reaction "birth defects" should be changed to "Common", and the Preferred Term should be changed to "foetal malformations" as follows:

Congenital, familial and genetic disorders:
Frequency ~~"Rare"~~ **"Common"** ~~birth defects~~ **foetal malformations**

Package Leaflet

Section 2. What you need to know before you take [XX]

Do not take [XX]
If you:

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

[…]

Warnings and precautions:

Talk to your doctor **or pharmacist** before taking [XX]
If you:

- **are pregnant or plan to become pregnant (see Section on "Pregnancy"). Due to the risk to the foetus, your treatment with [XX] must be discontinued immediately.**
- **are a woman of childbearing age (see also Section on "Pregnancy"). It is important to use effective contraception while you are taking this medicine.**

[…]

Pregnancy, breast-feeding and fertility

Pregnancy

Do not ~~use~~ **take [XX]** if you are pregnant, think you may be pregnant or trying to become pregnant. You should tell your doctor if you are planning to become pregnant.

Due to the possible risk of damage to the foetus, you must make sure you are not pregnant before starting treatment. Women who have not reached menopause ~~should~~ **must** use reliable contraception while they are taking this medicine.

Your doctor will make you aware of the risks if you do become pregnant while taking [XX] as it may cause a miscarriage, premature birth, abnormal formation of the foetus (birth defects). You should NEVER take this medicine if you are pregnant, as it can also have severe consequences on your child, especially on the heart, lungs and/or kidneys, including death. If you have received treatment with this medicine during pregnancy, talk with your doctor. If you decide to continue with the pregnancy, careful ultrasound scan monitoring of the pregnancy, with special attention to the limbs and head must be carried out.

Breast-feeding

Ask your doctor or pharmacist for advice before taking this medicine if you are breast-feeding. Do not use [XX] while you are breast-feeding.
~~Ask your doctor or pharmacist for advice before taking this medicine.~~

4. Possible side effects

~~Rare: may affect up to 1 in 1,000 people~~ **Common: may affect up to 1 in 10 people**
abnormal formation of foetus ~~birth defects~~.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this positio

Adoption of CMDh position:	March CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	5 May 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	4 July 2018