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 (systemic formulations), the scientific conclusions are as follows:

In view of available data on the use of diclofenac (systemic formulations) after pregnancy week 20 and the risk of renal dysfunction, oligohydramnios and neonatal renal impairment from the literature and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between use of diclofenac (systemic formulations) after pregnancy week 20 and the risk of renal dysfunction, oligohydramnios and neonatal renal impairment is at least a reasonable possibility. The PRAC concluded that the product information of products containing systemic formulations of diclofenac should be amended accordingly, if similar or stricter information regarding use in pregnancy is not already included.

In view of available data on Nicolau syndrome from the literature and spontaneous reports including in 5 cases with a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between intramuscular formulation of diclofenac and Nicolau syndrome is at least a reasonable possibility. The PRAC concluded that the product information of products containing intramuscular formulation of diclofenac should be added accordingly, if similar information regarding Nicolau syndrome is not already included.

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 (systemic formulations) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing diclofenac (systemic formulations) 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 (systemic formulations) 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~~)

All diclofenac products with systemic formulations

Summary of Product Characteristics

- Section 4.6

A warning should be amended as follows:

From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. During the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. **Antenatal monitoring for oligohydramnios should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios is found.**

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 **(see above)**;

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.

Consequently, diclofenac is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Package Leaflet

2. What you need to know before you <take/use> X

Pregnancy, breast-feeding and fertility

- Do not take <x> if you are in the last 3 months of pregnancy as it could harm your unborn child or cause problems at delivery. **It can cause kidney and heart problems in your unborn baby. It may affect your and your baby's tendency to bleed and cause labour to be later or longer than expected.** You should not take <x> during the first 6 months of pregnancy unless absolutely necessary **and advised by your doctor**. If you need treatment during this period or while you are trying to get pregnant, the lowest dose for the shortest time possible should be used. **From 20 weeks of pregnancy, <X> can cause kidney problems in your unborn baby, if taken for more than a few days, which can lead to low levels of amniotic fluid that surrounds the baby (oligohydramnios). If you need treatment for longer than a few days, your doctor may recommend additional monitoring.**

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Diclofenac products for intramuscular injection

Summary of Product Characteristics

- Section 4.4

A warning should be amended as follows:

General

The instructions for intramuscular injection should be strictly followed in order to avoid adverse events at the injection site, which may result in muscle weakness, muscle paralysis, hypoaesthesia**, embolia cutis medicamentosa (Nicolau syndrome)** and injection site necrosis.

A warning should be added or amended as follows:

Injection site reactions

Injection site reactions have been reported after the administration of diclofenac intramuscularly, including injection site necrosis and embolia cutis medicamentosa, also known as Nicolau syndrome (particularly after inadvertent subcutaneous administration). Appropriate needle selection and injection technique should be followed during intramuscular administration of diclofenac (see section [4.2 and/or 6.6 as appropriate]).

- Section 4.8

The following adverse reaction should be added under the SOC 'General disorders and administration site conditions' with a frequency 'Not known':

Embolia cutis medicamentosa (Nicolau syndrome)

Package Leaflet

4. Possible side effects

Some side effects can be serious

Tell the doctor straight away if you notice:

Injection site reactions including injection site pain, redness, swelling, hard lump, sores andbruising. This can progress to blackening and death of the skin and underlying tissues surrounding the injection site, that heal with scarring, also known as Nicolau syndrome.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	7 August 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	6 October 2022