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 dexketoprofen / tramadol the scientific conclusions are as follows:

In view of available data on the use of NSAIDs after pregnancy week 20 and the risk of "renal dysfunction, oligohydramnios and neonatal renal impairment" and "ductus arteriosus constriction" from literature and spontaneous reports, the PRAC (dexketoprofen PSUSA/00000997/202110) and CMDh (EMA/CMDh/642745/2022, Ibuprofen and use during pregnancy – type II variation DE/H/0392/II/032/G) concluded that the product information of products containing dexketoprofen should be amended accordingly.

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 dexketoprofen / tramadol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing dexketoprofen / tramadol 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 dexketoprofen / tramadol 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 4.6

Pregnancy

…

Dexketoprofen

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor 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 a prostaglandin synthesis inhibitor 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 give a prostaglandin synthesis inhibitor during the organogenetic period. Nevertheless, animal studies with dexketoprofen haven't shown reproductive toxicity (see 5.3).

From the 20th week of pregnancy onward, dexketoprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

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

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

….

Package Leaflet

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

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Dexketoprofen 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.
From 20 weeks of pregnancy, dexketoprofen can cause kidney problems in your unborn baby, that may lead to low levels of amniotic fluid that surrounds the baby (oligohydramnios) or narrowing of a blood vessel (ductus arteriosus) in the heart of the baby .
Tramadol is excreted into breast milk.
The use of <X> is contraindicated in pregnancy as well as during breast-feeding.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	31 October 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	29 December 2022