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 flurbiprofen, the scientific conclusions are as follows:

In view of available data on literature, on information about medicines of the same therapeutical class, on a plausible mechanism, the PRAC considers that a warning on possible masking effect of flurbiprofen (systemic, oromucosal formulations and transdermal patches) for the symptoms of infection, with consequent delay in the initiation of appropriate treatment and worsening of the infection, should be implemented. The PRAC concluded that the product information of products containing flurbiprofen for systemic use, oromucosal formulations and transdermal patches should be amended accordingly.

In view of available data on information about medicines of the same therapeutical class, on a plausible mechanism, the PRAC considers that a warning for topical flurbiprofen (oromucosal formulations and transdermal patches) for risk of use in pregnancy, should be implemented. The PRAC concluded that the product information of products containing flurbiprofen for oromucosal formulations and transdermal patches use 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 flurbiprofen the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing flurbiprofen 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 flurbiprofen 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 flurbiprofen products with systemic and oromucosal formulations and transdermal patches

Summary of Product Characteristics

4.2 Posology and methods of administration

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms **(see section 4.4).**

4.4 Special warnings and precautions for use

Masking of symptoms of underlying infections

Epidemiological studies suggest that systemic non-steroidal anti-inflammatory drugs (NSAIDs) can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When <product name> is administered while the patient suffers from fever or pain in relation to infection, monitoring of infection is advised.

Package Leaflet

Section 2 – warnings and precautions

Talk to your pharmacist or doctor if:

[…] **you have an infection - please see heading "Infections" below.**

[…]

Infections

Non-steroidal anti-inflammatory drugs (NSAIDs) may hide signs of infections such as fever and pain. This may delay appropriate treatment of infection, which may lead to an increased risk of complications. If you take this medicine while you have an infection and your symptoms of the infection persist or worsen, consult a doctor or pharmacist without delay.

Section 3 – How to use

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms. If you have an infection, consult a doctor or pharmacist without delay if symptoms (such as fever and pain) persist or worsen (see section 2).

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

All flurbiprofen products with oromucosal formulations and transdermal patches

In case the product information already includes a similar or stricter advice on use in pregnancy, the similar or stricter advice remains valid and should remain.

In case the product information contains statements indicating no teratogenic effects or no relevant systemic exposure this text should be deleted.

Summary of Product Characteristics

● Section 4.3

[…]

- third trimester of pregnancy

● Section 4.6

[…] **Pregnancy**

There are no clinical data from the use of [product name] during pregnancy. Even if systemic exposure is lower compared with oral administration, it is not known if the systemic [product name] exposure reached after topical administration can be harmful to an embryo/fetus. During the first and second trimester of pregnancy, [product name] should not be used unless clearly necessary. If used, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, systemic use of prostaglandin synthetase inhibitors including [product name] may induce cardiopulmonary and renal toxicity in the fetus. At the end of the pregnancy prolonged bleeding time in both mother and child may occur, and labour can be delayed. Therefore, [product name] is contraindicated during the last trimester of pregnancy (see section 4.3).

Package Leaflet

Section 2. What you need to know before you <take/use> [product name]

Do not use <product>

If you are in the last 3 months of pregnancy.

Pregnancy, breast-feeding and fertility

[…]

Oral forms (e.g. tablets) of flurbiprofen can cause adverse effects in your unborn baby. It is not known if the same risk applies to [product name].

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not use [product name] if you are in the last 3 months of pregnancy. You should not use [product name] during the first 6 months of pregnancy unless clearly necessary and advised by your doctor. If you need treatment during this period, the lowest dose for the shortest time possible should be used.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	3 September 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	2 November 2023