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 ibuprofen, ibuprofen lysine (not indicated in ductus arteriosus), ibuprofen / caffeine, the scientific conclusions are as follows:

The product information of **topical pharmaceutical forms of ibuprofen** should be updated (SmPC section 4.3, 4.6 and Package Leaflet, accordingly) to highlight the contraindication for use during the last trimester of pregnancy, as well as recommendations to avoid usage during the first and second trimester of pregnancy, unless clearly necessary, and if so use of the lowest possible dose, and for the shortest treatment duration.

With regards to **Kounis syndrome**, cumulatively, a total of 9 publications have been identified (3 published during the PSUR covering period) and other 6 between 2010 and 2020 (without confounders, and pointing towards a causal relationship between intake of ibuprofen and onset of Kounis syndrome). Having considered all the above, given a total of 9 suggestive cases, and considering that Kounis syndrome is an under-diagnosed life-threatening medical emergency (and health care porfessionals and patients would benefit from information in the product information of **systemic formulations of ibuprofen** about that, since adequate treatment could be initiated as early as possible after onset of the first symptoms), the available evidence is considered sufficient to establish a causal association between Kounis syndrome and ibuprofen and to warrant updates o SmPC seciton 4.4, 4.8 and package leaflet, accordingly.

Concerning **severe cutaneous adverse reactions (SCARs)**, despite lack of cases (perhaps due to under-reporting), PRAC considered that product information of topical ibuprofen-containing products warn already that systemic reactions (e.g. kidney damage) cannot be excluded even when the product is applied on the skin. There is indirect evidence that the risk of DRESS for certain drugs is dose dependent but there is no information whether it is the case with ibuprofen as well. On the other hand drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe adverse drug reaction. The clinical presentation is heterogeneous. The latency between drug initiation and onset of disease is prolonged, typically between two to eight weeks. DRESS is considered a T cell-mediated delayed hypersensitivity reaction. It is estimated to occur in 0.9 to 2 per 100,000 patients per year but the risk of developing DRESS varies from drug to drug. The suspected drug should be stopped immediately when the possibility of DRESS arises. This warning is very important especially in case of a non-prescription medicine. It is well known that NSAIDs including ibuprofen can cause DRESS. There are several spontaneous reports on systemic but also a few on topical formulation. The low frequency of this ADR and the underreporting can explain the very low number of reports in safety databases despite its extensive use. Therefore, as precautionary measure PRAC agreed to include DRESS also to the PI of topically used ibuprofen-containing medicinal products. Furthermore, taking into account the SCARs guideline, and considering that SCARs events are already listed in SmPC section 4.8 of several MAHs while some others have already updated also section 4.4, ultimately PRAC concluded that PI updates, aligned with the SCARs guideline, are deemed necessary for both **topical and systemic formulations of ibuprofen**.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for ibuprofen, ibuprofen lysine (not indicated in ductus arteriosus), ibuprofen / caffeine the CMDh is of the opinion that the benefit-risk balance of the

medicinal product(s) containing ibuprofen, ibuprofen lysine (not indicated in ductus arteriosus), ibuprofen / caffeine is unchanged subject to the proposed changes to the product information

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Topical formulations

Use during pregnancy -
Summary of Product Characteristics

- Section 4.3

/…/

- third trimester of pregnancy

- Section 4.6

[…] Pregnancy

There are no clinical data from the use of topical forms 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

…/

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.

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

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, as exemplified below, this text should be deleted (please see below):

~~Although there are no indications of teratogenic effects and the required systemic levels have not been reached,~~ the preparation should not be used during the first two thirds of pregnancy because of its effect on prostaglandin synthesis.

Systemic formulations

Kounis Syndrome

SmPC

Section 4.4

Cardiovascular and cerebrovascular effects

(…)

Cases of Kounis syndrome have been reported in patients treated with [product name]. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction-associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Section 4.8

Cardiac Disorders

Kounis syndrome (frequeny: *Not Known*)

Package leaflet

Section 2, Warnings and precautions

What you need to know before you take [product]

Signs of an allergic reaction to this medicine, including breathing problems, swelling of the face and neck region (angioedema), chest pain have been reported with ibuprofen. Stop immediately [product name] and contact immediately your doctor or medical emergencies if you notice any of these signs.

Section 4, Possible side effects

Chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome

Systemic and topical formulations

Severe cutaneous adverse reactions (SCARs)

SmPC

Section 4.4

~~Severe skin reactions~~ **Severe cutaneous adverse reactions (SCARs)**
~~Severe skin reactions~~, **Severe cutaneous adverse reactions (SCARs)**, ~~some with a fatal outcome, such as~~ including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), ~~and~~ Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), **and** acute generalized exanthematous pustulosis (AGEP), **which can be life-threatening or fatal**, have been reported in ~~connection~~ **association** with the use of ~~NSAIDs~~ **ibuprofen** (see section 4.8). ~~The risk of such reactions occurring is greatest at the beginning of the treatment,~~ **Most of these reactions occurred within** ~~the majority of cases occurring during~~ the first month. ~~Acute Generalised Exanthematous Pustulosis (AGEP) has been reported in relation to ibuprofen containing products.~~

If signs and symptoms suggestive of these reactions appear ibuprofen should be ~~discontinued~~ **withdrawn immediately and an alternative treatment considered (as appropriate).** ~~at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.~~

Section 4.8 [applicable to MAHs who do have the individual PTs listed]

Skin and subcutaneous tissue disorders

Very rare	**Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis)**
Not known	**Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)** **Acute generalised exanthematous pustulosis (AGEP)**

Package Leaflet

Section 2 - What you need to know before you use < product name **>**
Warnings and precautions - Take special care with <product name>:

Serious skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) have been reported in association with <ibuprofen> treatment. Stop using <product name> and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

Section 4 – Possible side effects
Stop using <ibuprofen> and seek medical attention immediately if you notice any of the following symptoms:

- **reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms [exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis].**
- **Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome).**
- **A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment (acute generalised exanthematous pustulosis).**

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

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	26 November 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	25 January 2024