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 dexibuprofen, the scientific conclusions are as follows:

In the view of available data on Kounis syndrome and severe cutaneous adverse reactions from the literature and spontaneous reports, including the PSUSA outcome for related active substance ibuprofen, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between dexibuprofen and Kounis syndrome and severe cutaneous adverse reactions is at least a reasonable possibility. The PRAC concluded that the product information of products containing dexibuprofen should be amended accordingly.

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 dexibuprofen the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing dexibuprofen 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)

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 4.4

A warning should be added as follows:

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.

~~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~~ **dexibuprofen** (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 dexibuprofen 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

Cardiac Disorders

Kounis syndrome (frequency: *Not known*)

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 take [product]

Warnings and precautions

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 dexibuprofen. Stop immediately [product name] and contact immediately your doctor or medical emergencies if you notice any of these signs.

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 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 *dexibuprofen* and seek medical attention immediately if you notice any of the following symptoms:

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

● 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:	April 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	09 June 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	08 August 2024