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:

Based on the review of literature and data from case reports and safety databases, the PRAC considers that a positive correlation between ‘anastomotic leak’ and diclofenac (systemic formulations) cannot be excluded and therefore recommends that a warning is added to section 4.4 of the summary of product characteristics. The package leaflet is updated accordingly.

Based on the review of literature and data from case reports and safety databases, the PRAC considers that a causal relationship between ‘kounis syndrome’ and diclofenac (systemic formulations) cannot be excluded and therefore recommends that this is added as a warning to section 4.4 and as an adverse drug reaction with a frequency ‘not known’ to section 4.8 of the summary of product characteristics. The package leaflet is updated 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 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~~)

Anastomotic leakage:

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Gastrointestinal effects:

[…]

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

[…]

Package Leaflet

Section 2: What you need to know before you take [product]

Tell your doctor if you recently had or you are going to have a surgery of the stomach or intestinal tract before receiving/taking/using [product name], as [product name] can sometimes worsen wound healing in your gut after surgery.

Kounis syndrome:

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

General:

[…]

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug. **Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.**

[…]

- Section 4.8

The following adverse reaction(s) should be added under the SOC Cardiac disorders with a frequency 'Not known': **Kounis syndrome**

Package Leaflet

Section 2: What you need to know before you take [product]

Some people MUST NOT use [product]. Talk to your doctor if:

- you think you may be allergic to diclofenac sodium, aspirin, ibuprofen or any other NSAID, or to any of the other ingredients of [product]. (These are listed at the end of the leaflet.) Signs of a hypersensitivity reaction include swelling of the face and mouth (angioedema), breathing problems, **chest pain**, runny nose, skin rash or any other allergic type reaction.

Section 4: Possible side effects

Tell your doctor immediately if you notice any of the following:

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

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	May 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	13 July 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	11 September 2019