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), the scientific conclusions are as follows:

[Only for systemic products or products with substantial systemic release: oral; rectal; IV; patch; vaginal]

i. Metabolic acidiosis (overdose):

"Metabolic acidosis" was reported in the period in three publications, renal tubular acidosis in two publications and acidosis (not specified) in one publication. These events were all (except one renal tubular acidosis) reported in a context of ibuprofen overdose. Causality between different types of NSAID overdose and metabolic acidosis appears to be established. This adverse event seems to be a potential risk in case of ibuprofen overdose and should be added in the corresponding sections of the product information.

ii. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):

Ibuprofen induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) appears to be a rare reported reaction. In the MAH safety database cases where ibuprofen was the only suspect drug and several more cases were identified where the association is possible or cannot be excluded. Further, there are several published cases describing an association between ibuprofen and DRESS.

Calculations of frequency for DRESS could not be correctly estimated, since it has only been obtained from clinical trial data with a low number of subjects involved (5589), and calculated based on guidance from the SmPC guideline. Therefore, the recommended frequency for DRESS should be described as 'not known'.

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 ibuprofen, ibuprofen lysine (not indicated in ductus arteriosus) 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) 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 ibuprofen, ibuprofen lysine (not indicated in ductus arteriosus) 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~~)

[Only for systemic products or products with substantial systemic release: oral; rectal; IV; patch; vaginal]

Summary of Product Characteristics

- Section 4.8, Undesirable effects

Skin and subcutaneous tissue disorders:

Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

Frequency: 'not known'

- Section 4.9, Overdose:

In serious poisoning metabolic acidosis may occur.

Package Leaflet

- 3. How to take < invented name>

If you take more < invented name> than you should

(Symptoms of Metabolic acidosis should be added to the currently approved text for overdose in Package Leaflet):

If you have taken more X than you should, or if children have taken this medicine by accident always contact a doctor or nearest hospital to get an opinion of the risk and advice on action to be taken.

The symptoms can include nausea, stomach pain, vomiting (may be blood streaked), headache, ringing in the ears, confusion and shaky eye movement. At high doses, drowsiness, chest pain, palpitations, loss of consciousness, convulsions (mainly in children), weakness and dizziness, blood in urine, cold body feeling, and breathing problems have been reported.

- 4. Possible side effects

(Drug reaction with eosinophilia and systemic symptoms):

A severe skin reaction known as DRESS syndrome can occur. Symptoms of DRESS include: skin rash, fever, swelling of lymph nodes and an increase of eosinophils (a type of white blood cells).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	23 December 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	21 February 2018