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 naproxen, the scientific conclusions are as follows:

In view of available data from the literature, spontaneous reports, including cases with a close temporal relationship and good documentation, the PRAC considers a causal relationship between naproxen and DRESS is at least a reasonable possibility. The PRAC concluded that the product information of products containing naproxen for systemic use should be amended accordingly.

Moreover, in view of the available data on the risk of fixed drug eruption (FDE) from numerous spontaneous reports and scientific literature, with positive re-challenge or confirmed oral provocation tests, and considering that several systemic naproxen-containing products already mentions this undesirable effect in the PI, the PRAC consider that a causal relationship between naproxen and FDE is well supported, and concluded that the product information of products containing naproxen for systemic use should be amended accordingly.

Finally, as precautionary measure, and in view of available information about medicines of the same therapeutic class, on a plausible mechanism the PI of naproxen-containing medicinal products for topical use should be updated with the wording on the risks of use during pregnancy, in line with the one adopted for topical ketoprofen, flurbiprofen and ibuprofen, ibuprofen lysine (not indicated in ductus arteriosus), ibuprofen / caffeine.

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

1. Recommendation on drug reaction with eosinophilia and systemic symptoms (DRESS) - for systemic formulations

The following changes to the product information of medicinal products containing the active substance naproxen for systemic formulations are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

The following text should be added to the existing place(s) where severe skin reactions (e.g. SJS and TEN) are listed in the existing paragraph regarding severe skin reactions in section 4.4 of the SmPC. If a similar wording is not already in place, it should be entirely implemented. In case the product information already includes a similar or stricter advice on SCARs, the similar or stricter advice remains valid and should remain.

Summary of Product Characteristics

For example, it can be added as follows, in case the product information contains the exact wording below:

- Section 4.4

Severe cutaneous adverse reactions (SCARs)

Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), **and drug reaction with eosinophilia and systemic symptoms (DRESS)**, which can be life-threatening or fatal, have been reported post-marketing in association with <*product name*> treatment. If signs and symptoms suggestive of these reactions appear, <*product name*> should be withdrawn immediately. If the patient has developed SJS, or TEN **or DRESS** with the use of <*product name*>, treatment with <*product name*> must not be restarted and should be permanently discontinued.

- Section 4.8

Skin and subcutaneous tissue disorders SOC

If DRESS is already included in section 4.8 with other frequency, the existing frequency should be maintained.

Frequency: Not known - **Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)**

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If the name of the individual serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis) are not mentioned in the paragraph regarding serious skin reactions in the current approved PL, there is no need for changes to this paragraph (i.e. no need to add the name 'drug reaction with eosinophilia and systemic symptoms (DRESS)' either).

Section 2 What you need to know before you take <product name>

Warning and precautions

Serious skin reactions including (Stevens-Johnson syndrome, toxic epidermal necrolysis, **drug reaction with eosinophilia and systemic symptoms (DRESS)**) have been reported in association with <*product name*>. 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 taking <product name> and immediately contact a doctor if you notice any of the following side effects:

Not known: frequency cannot be estimated from the available data

Widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS). See also section 2.

2. Recommendation on fixed drug eruption (FDE) - for systemic formulations

The following changes to the product information of medicinal products containing the active substance naproxen for systemic formulations are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of Product Characteristics

● Section 4.8

If FDE is already included in section 4.8 with other frequency, the existing frequency should be maintained.

Skin and subcutaneous tissue disorders SOC

Frequency: Not known **fixed drug eruption**

Package Leaflet

Section 4. Possible side effects

Stop taking <product name> and immediately contact a doctor if you notice any of the following side effects:

Not known: frequency cannot be estimated from the available data

a distinctive cutaneous allergic reaction known as fixed drug eruption, that usually recurs at the same site(s) on re-exposure to the medication and may look like round or oval patches of redness and swelling of the skin, blistering (hives), itching

3. Recommendation for use in pregnancy - for topical formulations

The following changes to the product information of medicinal products containing the active substance naproxen for topical formulations are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

This text is to be adapted, at a national level, to the existing wordings in the product information. 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 <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.

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:	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