Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisations

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSURs for cefuroxime sodium (except for intracameral use), the scientific conclusions are as follows:

In view of available data on DRESS and Kounis syndrome from the literature, spontaneous reports, including in some cases a close temporal relationship and in view of a plausible mechanism of action, the PRAC considers a causal relationship between cefuroxime sodium (except for intracameral use) and DRESS and Kounis syndrome to be at least a reasonable possibility. The PRAC concluded that the product information of cefuroxime sodium-containing products (except for intracameral use) should be amended accordingly.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisations

On the basis of the scientific conclusions for cefuroxime sodium (except for intracameral use), the CMDh is of the opinion that the benefit-risk balance of the medicinal products containing cefuroxime sodium (except for intracameral use) is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisations of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing cefuroxime sodium (except for intracameral use) 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 products

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

The MAHs shall ensure that the existing product information is amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below.

Summary of Product Characteristics

- **Section 4.4 Special warnings and precautions for use**

A warning should be amended as follows:

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. **There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).** In case of severe hypersensitivity reactions, treatment with cefuroxime must be discontinued immediately and adequate emergency measures must be initiated.

A warning should be added, under the paragraph regarding hypersensitivity reactions, as follows:

Severe cutaneous adverse reactions (SCARS)

Severe cutaneous adverse reactions including: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with cefuroxime treatment (see section 4.8).

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, cefuroxime should be withdrawn immediately and an alternative treatment considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of cefuroxime, treatment with cefuroxime must not be restarted in this patient at any time.

- **Section 4.8 Undesirable effects**

The following adverse reaction should be added under the SOC *Cardiac disorders* with a frequency 'unknown':

Kounis syndrome

The following adverse reaction should be added under the SOC *Skin and subcutaneous tissue disorders* with a frequency 'unknown':

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Package Leaflet

- **Section 2 What you need to know before you are given (product name)**

You must not be given (product name):

- **if you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after treatment with cefuroxime or any other cephalosporin antibiotics.**

Take special care with (product name)

Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with cefuroxime treatment. 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**

Conditions you need to look out for
A small number of people treated by (product name) get an allergic reaction or potentially serious skin reaction. Symptoms of these reactions include:

- **widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).**
- **chest pain in the context of allergic reactions, which may be a symptom of allergy triggered cardiac infarction (Kounis syndrome)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	17 February 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	19 May 2023