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 ceftriaxone, the scientific conclusions are as follows:

Given the available data on Kounis syndrome from the literature and spontaneous reports, including seven cases with a close temporal relationship, no confounding factors, and given a plausible mechanism of action, the PRAC considers a causal relationship between ceftriaxone and Kounis syndrome to be at least a reasonable possibility. The PRAC concluded that the product information of products containing ceftriaxone 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 ceftriaxone, the CMDh is of the opinion that the benefit-risk balance of the medicinal products containing ceftriaxone is unchanged subject to the proposed changes to the product information.

The CMDh recommends that the terms of the marketing authorisations should be varied.

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~~)

Summary of Product Characteristics

Section 4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). **Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8).** In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftriaxone, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if ceftriaxone is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Section 4.8 Undesirable effects

Cardiac disorders

Frequency **'Not known': Kounis syndrome**

Package Leaflet

Section 2. Warnings and precautions

What you need to know before you are given [product]

You must not be given <product name> if:

You have had a sudden or severe allergic reaction to penicillin or similar antibiotics (such as cephalosporins, carbapenems or monobactams). The signs include sudden swelling of the throat or face which might make it difficult to breath or swallow, sudden swelling of the hands, feet and ankles, **chest pain** and a severe rash that develops quickly.

4. Possible side effects

Conditions you need to look out for

Allergic reactions:

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:	January 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10/03/2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	09/05/2024