# 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 ceftriaxone, the scientific conclusions are as follows:

During the reporting interval a number of cases have been reported from spontaneous and literature reports for both adverse drug reactions 'Drug Reaction with Eosinophilia and Systemic Symptoms' (DRESS) and 'Jarisch-Herxheimer Reaction' (JAR). Based on the strength of evidence from spontaneous and literature reports it is sufficient to conclude on a causal relationship between both DRESS and JAR with the use of ceftriaxone. Therefore, a warning should be added in section 4.4 and 4.8 of the SmPC regarding the life-threatening or fatal DRESS, and also to ensure that the antibiotic treatment should not be discontinued in case of JHR symptoms. The package leaflet for medicinal products containing ceftriaxone should be 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 ceftriaxone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing ceftriaxone 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 ceftriaxone 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~~)

**Summary of Product Characteristics**

- Section 4.4

The following warnings should be added:

Hypersensitivity reactions

Severe cutaneous adverse reactions (Stevens Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis **and drug reaction with eosinophilia and systemic symptoms (DRESS)) which can be life-threatening or fatal**, have been reported **in association of ceftriaxone treatment**; however, the frequency of these events is not known (see section 4.8).

**Jarisch-Herxheimer reaction (JHR)**

**Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction (JHR) shortly after ceftriaxone treatment is started. JHR is usually a self – limiting condition or can be managed by symptomatic treatment. The antibiotic treatment should not be discontinued if such reaction occurs.**

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency `not known` **drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4).**

**Immune system disorders: Jarisch-Herxheimer reaction (frequency not known) (see section 4.4).**

**Package Leaflet**

Section 2 - What you need to know before you use ceftriaxone

Talk to your doctor or pharmacist or nurse before you are given <medicine> if:

- **You experience or have previously experienced a combination of any of the following symptoms: rash, red skin, blistering of the lips eyes and mouth, skin peeling, high fever, flu-like symptoms, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (signs of severe skin reactions, see also section 4 "Possible side effects").**

Section 4 – Possible side effects

Severe skin **reactions** (not known, frequency cannot be estimated from the available data)

If you get a severe skin **reaction**, tell a doctor straight away.

The signs may include:

- A severe rash that develops quickly, with blisters or peeling of the skin and possibly blisters in the mouth **(Stevens-Johnson syndrome and toxic epidermal necrolysis which are also known as SJS and TEN).**
- **A combination of any of the following symptoms: 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 or drug hypersensitivity syndrome).**
- **Jarisch-Herxheimer reaction which causes fever, chills, headache, muscle pain, and skin rash that is usually self-limiting. This occurs shortly after starting <….> treatment for infections with spirochete such as Lyme disease.**

## Annex III

## Timetable for the implementation of this position

**Timetable for the implementation of this position**

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| Adoption of CMDh position: | 30 January 2019 |
| Transmission to National Competent Authorities of the translations of the annexes to the position: | 17 March 2019 |
| Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): | 15 May 2019 |