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 cefoperazone, the scientific conclusions are as follows:

During the reporting period, the most frequent reported serious and non-serious adverse drug reactions were related to hypersensitivity and haemorrhages.

Further to a cumulative review of the Adverse Drug Reactions (ADRs) of haemorrhage/coagulopathy with the use of cefoperazone, the PRAC concluded that the provided dataset supports evidence of a relationship between serious, potentially fatal, cases of haemorrhage and the use of cefoperazone. Having considered the number of serious reports on haemorrhages and related events, together with the possible mechanism of evidence, the Committee concluded that the current warning on vitamin K deficiency with the use of cefoperazone containing medical products should be updated with information on a risk of haemorrhages and the risk factors. Hence, the PRAC is of the view that an amendment of the section 4.4 with a warning on haemorrhage needs to be made.

Therefore, in view of the data presented in the reviewed PSURs, the PRAC considered that changes to the product information of medicinal products containing cefoperazone were warranted.

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 cefoperazone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing cefoperazone 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 cefoperazone are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

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

A warning should be revised as follows:

~~As with other antibiotics, Vitamin K deficiency has occurred in a few patients treated with cefoperazone. The mechanism may possibly be related to the suppression of gut flora which normally synthesize this vitamin.~~ **Serious haemorrhage cases, including fatalities, have been reported with cefoperazone.** Those at risk include patients with poor diet, malabsorption states ~~(e.g. cystic fibrosis)~~ and patients on prolonged intravenous alimentation regimens. ~~Prothrombin time should be monitored in these patients and exogenous vitamin K administered as indicated.~~ **These patients should be monitored for signs of bleeding, thrombocytopenia, and hypoprothrombinemia. Cefoperazone should be discontinued if there is persistent bleeding and no alternative explanations are identified.**

Package Leaflet

2. Warnings and precautions

Cefoperazone - active substance of <product name> – may inhibit blood clotting. Serious bleedings, including fatal, have been reported with <product name>. Please contact your physician immediately if you experience any sign of bleeding.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2016 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	29 October 2016
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	28 December 2016