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 flucloxacillin, the scientific conclusions are as follows:

In view of available data on the risk of **Hypokalaemia** from the literature and spontaneous reports and also in view of a plausible mechanism of action, the Lead Member State considers that a causal relationship between flucloxacillin and hypokalaemia is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing flucloxacillin should be amended accordingly.

In view of available data on **Oesophageal pain and related events** from the literature and spontaneous reports, including a close temporal relationship in some cases and a positive de-challenge in 10 cases, and also in view of a plausible mechanism of action, the Lead Member State considers that a causal relationship between flucloxacillin oral formulations and oesophageal pain and related events is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing oral formulations of flucloxacillin 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 Authorisation(s)

On the basis of the scientific conclusions for flucloxacillin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing flucloxacillin 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 flucloxacillin 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) For ALL formulations of flucloxacillin-containing medicinal products:

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Hypokalaemia (potentially life threatening) can occur with the use of flucloxacillin, especially in high doses. Hypokalaemia caused by flucloxacillin can be resistant to potassium supplementation. Regular measurements of potassium levels are recommended during the therapy with higher doses of flucloxacillin. Attention for this risk is warranted also when combining flucloxacillin with hypokalemia-inducing diuretics or when other risk factors for the development of hypokalemia are present (e.g. malnutrition, renal tubule disfunction).

- Section 4.8

The following adverse reaction(s) should be added under the SOC Metabolism and nutrition disorders with a frequency not known (cannot be estimated from the available data):

Hypokalaemia

Package Leaflet

- Section 2. What you need to know before you <take> <use> X

Warnings and precautions

Talk to your doctor <or> <,> <pharmacist> <or nurse> before <taking> <using> X:

The use of flucloxacillin, especially in high doses, may reduce the potassium levels in the blood (hypokalaemia). Your doctor may measure your potassium levels regularly during the therapy with higher doses of flucloxacillin.

- Section 4. Possible side effects

Not known (cannot be estimated from the available data):

- Low potassium levels in the blood (hypokalaemia), which can cause muscle weakness, twitching or abnormal heart rhythm.

2) For ORAL formulations of flucloxacillin-containing medicinal products:

Summary of Product Characteristics

- Section 4.2

Method of administration

[For Capsules and Tablets formulations]

[INVENTED NAME] [pharmaceutical form] should be taken at least 1 hour before or 2 hours after meals.

The [pharmaceutical form] should be taken with a full glass of water (250 ml), to reduce the risk of oesophageal pain (see section 4.8).

Patients should not lay down immediately after [INVENTED NAME] intake.

[For Powder for oral suspension formulation]

[INVENTED NAME] powder for oral suspension should be taken at least 1 hour before or 2 hours after meals.

A full glass of water (250 ml) should be taken afterwards, to reduce the risk of oesophageal pain (see section 4.8). Patients should not lay down immediately after [INVENTED NAME] intake.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Gastrointestinal disorders with a frequency not known (cannot be estimated from the available data):

[For All oral formulations]

Oesophageal pain and related events *

*** oesophagitis, burn oesophageal, throat irritation, oropharyngeal pain or oral pain**

Package Leaflet

- Section 3. How to <take> <use> X

[For Capsules and Tablets formulations]

Take your flucloxacillin [pharmaceutical form] at least 1 hour before or 2 hours after meals.

To reduce the risk of pain in your oesophagus (the tube that connects your mouth with your stomach) swallow [pharmaceutical form] with a full glass of water (250 ml) and do not lie down immediately after taking your [pharmaceutical form].

[For Powder for oral suspension formulation]

Take your powder for oral suspension at least 1 hour before or 2 hours after meals.

To reduce the risk of pain in your oesophagus (the tube that connects your mouth with your stomach) take a full glass of water (250ml) after oral suspension intake and do not lie down immediately after oral suspension intake.

- Section 4. Possible side effects

[For All oral formulations]

Not known (cannot be estimated from the available data):

- Pain in oesophagus (the tube that connects mouth with stomach) and other related symptoms, such as difficulties in swallowing, heartburn, throat irritation or chest pain.

Annex III

Timetable for the implementation of this position>

Timetable for the implementation of this position

Adoption of CMDh position:	November 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 December 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	25 February 2021