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 amoxicillin, the scientific conclusions are as follows:

In view of available data on risks from the literature, spontaneous reports including some cases of close temporal relationship, the PRAC considers a causal relationship between amoxicillin and aseptic meningitis, Kounis syndrome, crystalluria (including acute renal injury), drug-induced enterocolitis syndrome (DIES) and linear IgA disease, as well as drug-drug interactions between amoxicillin and methotrexate and between amoxicillin and probenecid to be at least a reasonable possibility. The PRAC concluded that the product information of amoxicillin-containing products 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 amoxicillin, the CMDh is of the opinion that the benefit-risk balance of the medicinal products containing amoxicillin 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 amoxicillin 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**

The existing warning should be revised as follows:

Serious and occasionally fatal hypersensitivity reactions (including **anaphylactoid** ~~non-allergenic hypersensitivity~~ and severe cutaneous reactions) have been reported in patients on penicillin therapy. **Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8).** These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin therapy must be discontinued and appropriate alternative therapy instituted.

A warning should be added as follows:

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug <intake> <administration> <use>) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

The existing warning should be revised as follows:

In patients with reduced urine output, crystalluria **(including acute renal injury)** has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see section**s 4.8 and** 4.9).

- **Section 4.5 Interaction with other medicinal products and other forms of interaction**

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin.

- **Section 4.8 Undesirable effects**

The following adverse reactions should be added:

- under the SOC *Skin and subcutaneous tissue disorders,* with a frequency 'not known': **Linear IgA disease**

- under the SOC *Nervous system disorders*, with a frequency 'not known': **Aseptic meningitis**
- under the SOC *Cardiac disorders,* with a frequency 'not known': **Kounis syndrome**
- under the *SOC Gastrointestinal disorders,* with a frequency 'not known': **Drug-induced enterocolitis syndrome**
- under the SOC *Renal and urinary tract disorders* with a frequency 'not known': Crystalluria **(including acute renal injury)**

- **Section 4.9 Overdose**

The following information should be added:

- **Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).**

Package Leaflet

- **Section 2 What you need to know before you are given Amoxicillin**

Methotrexate (used to treat cancer and severe psoriasis), penicillins may reduce the excretion of methotrexate causing a potential increase in side effects.

Probenecid (used to treat gout), concomitant use of probenecid may reduce the excretion of amoxicillin and is not recommended.

- **Section 4 Possible side effects**

Chest pain in the context of allergic reactions, which may be a symptom of allergy triggered cardiac infarction (Kounis syndrome)

Drug-induced enterocolitis syndrome (DIES):
DIES has been reported mainly in children receiving amoxicillin. It is a certain kind of allergic reaction with the leading symptom of repetitive vomiting (1-4 hours after drug <intake> <administration> <use>). Further symptoms could comprise abdominal pain, lethargy, diarrhoea, and low blood pressure.

Crystals in urine **leading to acute renal injury**

Rash with blisters arranged in a circle with central crusting or like a string of pearls (linear IgA disease)

Inflammation of the membranes that surround the brain and spinal cord (aseptic meningitis)

\

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	4 January 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	23 February 2023