

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/clavulanate, the scientific conclusions are as follows:

In view of available data from the literature and spontaneous reports including in some cases a close temporal relationship, a positive dechallenge and/or rechallenge, the PRAC considers a causal relationship between amoxicillin/clavulanate and “linear IgA disease”, “aseptic meningitis”, “Kounis syndrome”, “pancreatitis acute”, “drug-induced enterocolitis syndrome” and “crystalluria (including acute renal injury)” is at least a reasonable possibility. The PRAC concluded that the product information of products containing amoxicillin/clavulanate 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/clavulanate the CMDh is of the opinion that the benefit-risk balance of the medicinal products containing amoxicillin/clavulanate 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/clavulanate 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 and severe cutaneous adverse 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/clavulanic acid 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/clavulanate (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 sections **4.8 and 4.9**).

- **Section 4.8 Undesirable effects**

The following adverse reactions should be added/revised:

- 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 *Gastrointestinal disorders*, with a frequency ‘not known’: **Pancreatitis acute**

- under the SOC *Renal and urinary tract disorders* with a frequency ‘not known’: Crystalluria
(including acute renal injury)

Package Leaflet

- **Section 4 Possible side effects**

Conditions you need to look out for

Allergic reactions:

- skin rash
- inflammation of blood vessels (vasculitis) which may be visible as red or purple raised spots on the skin, but can affect other parts of the body
- fever, joint pain, swollen glands in the neck, armpit or groin
- swelling, sometimes of the face or throat (angioedema), causing difficulty in breathing
- collapse
- **chest pain in the context of allergic reactions, which may be a symptom of allergy triggered cardiac infarction (Kounis syndrome)**

→ Contact a doctor immediately if you get any of these symptoms. Stop <taking><using> [Invented Name].

Inflammation of large intestine

Inflammation of the large intestine, causing watery diarrhoea usually with blood and mucus, stomach pain and/or fever.

Acute inflammation of the pancreas (acute pancreatitis)

If you have severe and on-going pain in the stomach area this could be a sign of acute pancreatitis.

Drug-induced enterocolitis syndrome (DIES):

DIES has been reported mainly in children receiving amoxicillin/clavulanate. 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.

→ Contact your doctor as soon as possible for advice if you get these symptoms

Frequency not known (Frequency cannot be estimated from the available data)

Crystals in urine **leading to acute kidney 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:	10 November 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	04 January 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	23 February 2023