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 allopurinol the scientific conclusions are as follows:

In view of available data from literature on the fact that allopurinol should be introduced at low dosage, e.g. 100 mg/day to reduce the risk of adverse reactions the, the PRAC concluded that the product information of products containing allopurinol should be amended accordingly, if similar information is not already included in their product information.

In view of available data on aseptic meningitis, from the literature and the spontaneous reports, which include a close temporal relationship, a positive de-challenge and/or re-challenge, the PRAC considers a causal relationship between allopurinol and aseptic meningitis at least possible. The PRAC concluded that the product information of products containing allopurinol should be amended accordingly.

In view of available data on diarrhoea, from the already existing product information of some products provided in this procedure and a substantial number of spontaneous reports, the PRAC considers a causal relationship between oral formulations of allopurinol and diarrhoea at least possible. The PRAC concluded that the product information of products containing oral formulations of allopurinol 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 allopurinol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing allopurinol 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 allopurinol 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 4.2

Allopurinol should be introduced at low dosage, e.g. 100 mg/day, to reduce the risk of adverse reactions and increased only if the serum urate response is unsatisfactory. Extra caution should be exercised if renal function is poor.

- Section 4.8

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

Aseptic meningitis

The following adverse reaction should be added under the SOC gastrointestinal disorders with a frequency uncommon:

Diarrhoea

Package Leaflet

- Section 3

You doctor will usually start with a low dose of allopurinol (e.g. 100 mg/day), to reduce the risk of possible side effects. Your dose will be increased if necessary.

- Section 4

The following adverse reaction should be added with a frequency not known (cannot be estimated from available data):

Aseptic meningitis (inflammation of the membranes that surround the brain and spinal cord): symptoms include neck stiffness, headache, nausea, fever or consciousness clouding. Seek medical attention immediately if these occur.

[…]

The following adverse reaction should be added with frequency uncommon:

Diarrhoea

[…]

Annex III

Timetable for the implementation of this position>

Timetable for the implementation of this position

Adoption of CMDh position:	September CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	31 October 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 December 2021