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 on lichenoid drug reaction and cytopenia due to drug-drug interactions of azathioprine/mercaptopurine with allopurinol from the literature and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between allopurinol and lichenoid drug reaction as well as cytopenia due to drug-drug interactions of azathioprine/mercaptopurine with allopurinol is at least a reasonable possibility. The PRAC concluded that the product information of products containing allopurinol should be amended accordingly. For authorised products which already have a warning in Sections 4.4 and in 4.5 of the SmPC, the more stringent wording should be kept.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

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 recommends that the terms of the marketing authorisation(s) should be varied.

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

Concomitant use of allopurinol with 6-mercaptopurine or azathioprine should be avoided as there have been reports of fatal cases (see section 4.5).

- Section 4.5

An interaction should be amended as follows:

6-mercaptopurine and azathioprine

Azathioprine is metabolised to 6-mercaptopurine, which is inactivated by the action of xanthine oxidase. When 6-mercaptopurine or azathioprine is given concurrently with allopurinol**, a xanthine oxidase inhibitor**, inhibition of xanthine oxidase will prolong their activity. **Serum concentrations of 6-mercaptopurine or azathioprine may reach toxic levels with consequent life-threatening pancytopenia and myelosuppression when these medicinal products are given concurrently with allopurinol. Therefore, concomitant use of allopurinol with 6-mercaptopurine or azathioprine should be avoided. If it is determined that co-administration with 6-mercaptopurine or azathioprine is clinically needed, dosing should be reduced to one quarter (25%) of the usual dose of 6-mercaptopurine or azathioprine and frequent haematologic monitoring should be ensured (see section 4.4).**

Patients should be advised to report any signs or symptoms of bone marrow suppression (unexplained bruising or bleeding, sore throat, fever).

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency not known:

Lichenoid drug reaction

Package Leaflet

2. What you need to know before you take [allopurinol product name]

Other medicines and [allopurinol product name]

It is especially important to tell your doctor if you are taking any of the medicines listed below. Your doctor may need to reduce the dose of your medicine and/or monitor you more carefully because of the increased risk of side effects when [allopurinol product name] is taken at the same time as:

[…]

- 6-Mercaptopurine (used to treat blood cancer)
- Azathioprine (used to suppress the immune system)

The co-administration of 6-mercaptopurine or azathioprine with allopurinol should be avoided. When 6-mercaptopurine or azathioprine is given concurrently with [allopurinol product name], the dose of 6-mercaptopurine or azathioprine should be reduced because their activity will be prolonged. This could increase the risk of serious blood disorders. In this case, your doctor will closely monitor your blood count during treatment.

Seek medical advice immediately if you notice that you have any unexplained bruising, bleeding, fever or sore throat.

[…]

4. Possible side effects

Not known (cannot be estimated from available data): **Lichenoid skin rash (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes)**

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:	3 November 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	2 January 2025