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:

Severe cutaneous adverse reactions (SCARs), like Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic syndromes (DRESS) can occur rarely with allopurinol and are known side effects. Based on the reviewed available literature, correlation to the HLA-B*5801 allele has been found but of different intensity in different populations. Especially from the Han Chinese, Thai and Korean population a high frequency of the HLA-B*5801 allele was found, whereas frequency is rather low in the European and Japanese population. Additional knowledge on Han Chinese, Thai patients or Koreans with chronic renal insufficiency and benefit of screening for HLA-B*5801 before starting allopurinol was also reviewed and the evidence for the effectiveness of HLA-B*5801 genotype screening to minimise the risk of allopurinol-induced SCAR in population subgroups with Asian descend (Han Chinese, Thai, Korean) is considered sufficient. The PRAC therefore considered revising the existing wording included in section 4.4 of the Summary of Product Characteristics (SmPC) and section 2 of the package leaflet (PL) to reflect the most recent knowledge about Asian subpopulations on the risk of developing allopurinol related SCARs. In addition, based on literature reviewed during the period and taking into account that the product information of febuxostat already contains information related to increased thyroid stimulating hormone (TSH) levels in patients on long term treatment, the PRAC considered that sections 4.4 and 4.8 of the SmPC of allopurinol should be updated to include this information. Further, based on literature as well as post marketing data reviewed during the period, the PRAC considered that section 4.5 of the SmPC should be updated to include an interval of at least 3 hours between taking aluminium hydroxide and allopurinol due to the attenuated effect of allopurinol when administered together. In addition, information on the concomitant administration of allopurinol and cytostatics should be included in section 4.5 in order to better inform physicians that the patient's blood count should be monitored in these cases. Further, as allopurinol is excreted in the breast milk and there is a hypothetic risk for adverse reactions, even allergic reactions, in infants, allopurinol should not be used in breast feeding and therefore this information should be included in section 4.6 of the SmPC. Finally, the PRAC considered updating section 4.8 of the SmPC to include agranulocytosis, thrombocytopenia and aplastic anaemia. The PL is updated 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 4.4 Special warnings and precautions for use:

[The following text should be revised as follows]

[…]

The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The frequency of the HLA-B*5801 allele varies widely between ethnic populations: up to 20% in Han Chinese population, **8-15% in the Thai,** about 12% in the Korean population and 1-2% in individuals of Japanese or European origin.

[…]

[The following text should be revised as follows]

[…]

~~The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established.~~ **Screening for HLA-B*5801 should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high. Chronic kidney disease may increase the risk in these patients additionally In case that no HLA-B*5801 genotyping is available for patients with Han Chinese, Thai or Korean descent the benefits should be thoroughly assessed and considered outweigh the possible higher risks before starting therapy. The use of genotyping has not been established in other patient populations.**

If the patient is a known carrier for HLA-B*5801 **(especially in those who are from Han Chinese, Thai or Korean descent**, ~~the use of allopurinol may be considered if~~ **allopurinol should not be started unless there are no other reasonable therapeutic options and** the benefits are thought to exceed the risk. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.

SJS/TEN can still occur in patients who are found to be negative for HLA-B*5801 irrespective of their ethnic origin.

[…]

[A warning should be added as follows]

Thyroid disorders

Increased TSH values (>5.5 µIU/mL) were observed in patients on long-term treatment with allopurinol (5.8%) in a long term open label extension study. Caution is required when allopurinol is used in patients with alteration of thyroid function.

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

[The following text should be added as follows]

Cytostatics

With administration of allopurinol and cytostatics (e.g. cyclophosphamide, doxorubicin, bleomycin, procarbazine, alkyl halogenides), blood dyscrasias occur more frequently than when these active substances are administered alone.

Blood count monitoring should therefore be performed at regular intervals.

[The following text should be added as follows]

Aluminium hydroxide

If aluminium hydroxide is taken concomitantly, allopurinol may have an attenuated effect. There should be an interval of at least 3 hours between taking both medicines.

- Section 4.6 Fertility, pregnancy and lactation

[The following text should be added as follows]

Breastfeeding

Allopurinol and its metabolite oxipurinol is excreted in the human breast milk. Allopurinol during breastfeeding is not recommended.

- Section 4.8 Undesirable effects

[The following adverse reactions should be added with a frequency very rare]

Blood and lymphatic system disorders: agranulocytosis, thrombocytopenia and aplastic anemia.

Very rare reports have been received of thrombocytopenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal and/or hepatic function, reinforcing the need for particular care in this group of patients.

[The following adverse reaction should be added with a frequency common]

Investigations: blood thyroid stimulating hormone increased*

***The occurrence of increased thyroid stimulating hormone (TSH) in the relevant studies did not report any impact on free T4 levels or had TSH levels indicative of subclinical hypothyroidism.**

Package leaflet

- Section 2

[The following text should be revised as follows]

[…]

These serious skin reactions can be more common in people of Han Chinese, Thai **or Korean** origin. **Chronic kidney disease may increase the risk in these patients additionally.**

[…]

[The following text should be added as follows under Other medicines and Allopurinol tablets]

If aluminium hydroxide is taken concomitantly, allopurinol may have an attenuated effect. There should be an interval of at least 3 hours between taking both medicines.

[…]

With administration of allopurinol and cytostatics (e.g. cyclophosphamide, doxorubicin, bleomycin, procarbazine, alkyl halogenides), blood dyscrasias occur more frequently than when these active substances are administered alone.

Blood count monitoring should therefore be performed at regular intervals.

[The following text should be added as follows under Pregnancy and breastfeeding]

Allopurinol is excreted in the human breast milk. Allopurinol during breastfeeding is not recommended.

- Section 4

[The following adverse drug reaction should be added with a frequency common (may affect up to 1 in 10 people)]

Increased level of thyroid stimulating hormone in the blood.

[The following adverse drug reaction should be added with a frequency very rare (may affect up to 1 in 10,000 people)]

Occasionally Allopurinol tablets may affect your blood, which can manifest as bruising more easily than usual, or you may develop a sore throat or other signs of an infection. These effects usually occur in people with liver or kidney problems. Tell your doctor as soon as possible.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	28 October 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	27 December 2017