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 azathioprine, the scientific conclusions are as follows:

Sweet's syndrome (Acute febrile neutrophilic dermatosis):

Based on the review of literature and data from case reports and safety databases, the PRAC considers that a positive correlation between 'Sweet's syndrome (Acute febrile neutrophilic dermatosis)' and azathioprine cannot be excluded and therefore recommends that it is added as an adverse drug reaction with a frequency 'not known' to section 4.8 of the summary of product characteristics. The package leaflet is updated accordingly.

Interaction between azathioprine and febuxostat:

Based on the review of literature and data from case reports and additional data sources, the PRAC considers that it cannot be excluded that there is drug interaction between azathioprine and febuxostat and therefore recommends that a text is added to section 4.5 of the summary of product characteristics. The package leaflet is updated accordingly.

Interactions with Neuromuscular blocking agents:

Based on the review of literature and data from other sources, the PRAC considers that it cannot be excluded that there is drug interaction between azathioprine and neuromuscular agents and therefore recommends that a text is added in section 4.5 with a cross referenced warning in section 4.4 of the summary of product characteristics. The package leaflet 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 azathioprine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing azathioprine 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 azathioprine 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

For SmPCs that do not already have this information, warnings should be added as follows:

- Section 4.4

Neuromuscular blocking agents
Special care is necessary when azathioprine is given concomitantly with neuromuscular blocking agents such as atracurium, rocuronium, cisatracurium or suxamethonium (also known as succinylcholine) (see section 4.5). Anesthesiologists should check whether their patients are administered azathioprine prior to surgery.

- Section 4.5

Neuromuscular blocking agents
There is clinical evidence that azathioprine antagonises the effect of non-depolarising muscle relaxants. Experimental data confirm that azathioprine reverses the neuromuscular blockade produced by non-depolarising agents, and show that azathioprine potentiates the neuromuscular blockade produced by depolarising agents (see section 4.4

For SmPCs that do not already have this information, a warning should be added as follows:

- Section 4.5

Allopurinol/oxipurinol/thiopurinol **and other xanthine oxidase inhibitors**
Based on non-clinical data, other xanthine oxidase inhibitors, such as febuxostat, may prolong the activity of azathioprine possibly resulting in enhanced bone marrow suppression. Concomitant administration is not recommended as data are insufficient to determine an adequate dose reduction of azathioprine.

MAHs with the below term already included in their product information section 4.8 should maintain their calculated frequency:

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin reactions and subcutaneous tissue disorders with a frequency 'not known': **Acute febrile neutrophilic dermatosis (Sweet's syndrome)**

Package Leaflet

- 2. What you need to know before you take [Product name]

Other medicines and [product name]

[….]

- methotrexate (mainly used to treat cancers)
- allopurinol, oxipurinol, thiopurinol **or other xanthine oxidase inhibitors, such as febuxostat** (mainly used to treat gout)
- penicillamine (mainly used in the treatment of rheumatoid arthritis)
- […]
- infliximab (mainly used in the treatment of ulcerative colitis and Crohn's disease)
- **Before a surgical procedure tell the anesthesiologist that you are taking azathioprine because muscle relaxants used during anesthesia may interact with azathioprine**

- 4. Possible side effects

If you get any of the following serious side effects, talk to your doctor or specialist doctor immediately, you may need urgent medical treatment:

[….]

- various types of cancers including blood, lymph and skin cancers (see section 2 Warnings and precautions) (these may be rare side effects which may affect up to 1 in 1000 people).
- **You may develop a rash (raised red, pink or purple lumps which are sore to touch), particularly on your arms, hands, fingers, face and neck, which may also be accompanied by a fever (Sweet's syndrome, also known as acute febrile neutrophilic dermatosis). The rate at which these side effects occur is not known (cannot be estimated from available data).**
- a certain type of lymphomas (hepatosplenic T-cell lymphoma)….

[…]

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	08/09/2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	07/11/2019