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 trimethoprim, the scientific conclusions are as follows:

In view of available data on the literature and spontaneous reports and in view of a plausible mechanism of action, the PRAC Lead Member State considers a causal relationship between trimethoprim and **drug reaction with eosinophilia and systemic symptoms (DRESS)** is at least a reasonable possibility. The PRAC Lead Member State concluded that the product information of products containing trimethoprim should be amended accordingly.

In view of available data on the literature and spontaneous reports and in view of a plausible mechanism of action, the PRAC Lead Member State considers a causal relationship between trimethoprim and congenital malformations / spontaneous abortions is at least a reasonable possibility. The PRAC Lead Member State concluded that the product information of products containing trimethoprim should be amended to contraindicate trimethoprim during the **first trimester of pregnancy**.

In view of available data on the literature and spontaneous reports, the PRAC Lead Member State considers a causal relationship between trimethoprim and **hallucinations** is at least a reasonable possibility. The PRAC Lead Member State concluded that the product information of products containing trimethoprim should be amended accordingly.

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 trimethoprim the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing trimethoprim 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**

A warning should be added as follows:

Severe cutaneous adverse reactions (SCARs)

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with trimethoprim treatment (see section 4.8).

Patients should be advised of the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of these reactions appear, trimethoprim should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of trimethoprim, the treatment must not be restarted in this patient at any time.

- **Section 4.8**

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

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Package Leaflet

- **Section 2 - What you need to know before you use <medicine>**

TELL YOUR DOCTOR BEFORE TAKING <medicine>:

• If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking trimethoprim.

Warnings and precautions - Take special care with <medicine>:

Serious skin reactions, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with trimethoprim treatment. Stop using trimethoprim and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

- **Section 4 – Possible side effects**

Stop using trimethoprim and seek medical attention immediately if you notice any of the following symptoms:

• reddish patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN)).

• Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome)

Summary of Product Characteristics

- **Section 4.3 Contraindications**

The contraindications should be amended as follows (stricter existing advice may remain):

First trimester of pregnancy (see section 4.6).

- **Section 4.6**

New information with regards to the risk(s) of the product when used during pregnancy should be added as follows (stricter existing advice may remain):

Pregnancy:

Trimethoprim is contraindicated during the first trimester of pregnancy (see section 4.3). Studies in animals have shown a teratogenic effect.

Epidemiological studies have shown an increased risk of spontaneous abortion and congenital malformations, in particular neural tube defects, oral clefts and cardiovascular defects, in children of mothers treated with trimethoprim during the first trimester of pregnancy. The presumed mechanism of action is thought to be interference with folates.

In the second and third trimesters, use should be avoided, unless clinically necessary.

Package Leaflet

(Stricter existing advice may remain):

- **Section 2 – Do not use <medicine>:**

If you are pregnant (first 3 months) or might be pregnant

- **Section 2 "Pregnancy and breast-feeding"**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

This medicine should not be taken during first three months of pregnancy. Treatment with trimethoprim in the first three months of pregnancy may increase the risk of miscarriage. Children born to mothers treated with trimethoprim during the first trimester of pregnancy may have an increased risk of birth defects, in particular neural tube defects (where the spine and spinal cord do not form properly), oral clefts (where the lip and palate do not form properly) and defects affecting the heart.

Summary of Product Characteristics

- **Section 4.8**

The following adverse reaction(s) should be added under the SOC "Psychiatric disorders" with a frequency "very rare":

Hallucinations.

Package Leaflet

- **Section 4 – Possible side effects**

Hallucinations.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	12 November 2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	29 January 2026