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 promethazine, the scientific conclusions are as follows:

In view of available data on risks from the literature, spontaneous reports, including in some cases a close temporal relationship, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between promethazine and psychiatric and neurologic adverse drug reactions, neuroleptic malignant syndrome, QT prolongation (including Torsade de pointes), thrombocytopenia (for those medicinal products that do not already list a broader term such as blood dyscrasias), and the potential for tissue damage associated with intravenous administration is at least a reasonable possibility. The PRAC concluded that the product information of products for systemic administration (oral formulations and parenteral formulations) containing promethazine 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 promethazine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing promethazine 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~~)

Oral formulations:

Summary of Product Characteristics

Section 4.4

A warning should be added as follows:

QT interval

As phenothiazines can prolong the QT interval, caution is advised in treated patients with pronounced bradycardia, cardiovascular disease, with a hereditary form of prolongation of the QT interval and concomitant use with other products leading to QT prolongation.

- Section 4.5

Special caution is required when promethazine is used concurrently with other products leading to QT prolongation, including medicinal products such as antipsychotics, i.e., some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, amisulpride, tiapride), pimozide, haloperidol, droperidol, citalopram, halofantrin, methadone, pentamidine, and moxifloxacine.

- Section 4.8

The following adverse reactions should be added under the SOC Cardiac disorders with a frequency “not known”:

QT prolongation, Torsade de pointes

The following adverse reactions should be added under the SOC Nervous system disorders with a frequency “not known”:

neuroleptic malignant syndrome, psychomotor hyperactivity

The following adverse reactions should be added under the SOC Psychiatric disorders with a frequency “not known”:

hallucinations, aggression

The following adverse reactions should be added under the SOC Blood and lymphatic system disorders with a frequency “not known”:

thrombocytopenia

- Section 4.9

The recommendations for signs and symptoms of overdose should be amended as follows:

Prolonged QT interval and cases of severe arrhythmias with fatal outcome have been described in overdose of phenothiazines.

Package Leaflet

- Section 2

  Warnings and precautions for use

  Check with your doctor of nurse before having <Medicinal product> if:

  You have any serious heart problems

  You have any personal or family history of heart disease

  You have an irregular heartbeat

  Other medicines and *[…]*

Also tell your doctor or pharmacist if you are taking, have recently taken or might take any of the following:

medicines that can affect your heart rhythm

- Section 4

Frequency “not known (cannot be estimated from the available data)”:

Abnormal electrical activity of the heart that affects its rhythm, including life-threatening rhythm disturbance

A serious reaction with fever, rigid muscles, changing blood pressure and coma (neuroleptic malignant syndrome)

Low levels of blood platelets (which can lead to bleeding and bruising)

Restlessness

Hallucinations

Aggression

Parenteral formulations:

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Tissue injury, including gangrene

Intravenous injection should be performed with extreme care to avoid extravasation or inadvertent intra-arterial injection, which could lead to necrosis and peripheral gangrene. If a patient complains of pain during intravenous injection, stop the injection immediately, as this may be a sign of extravasation or inadvertent intra-arterial injection. Intramuscular injection must also be performed carefully to avoid inadvertent subcutaneous injection, which could lead to local necrosis.

QT interval

As phenothiazines can prolong the QT interval, caution is advised in treating patients with pronounced bradycardia, cardiovascular disease, with a hereditary form of prolongation of the QT interval and concomitant use with other products leading to QT prolongation.

- Section 4.5

Special caution is required when promethazine is used concurrently with other products leading to QT prolongation, including medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, amisulpride, tiapride), pimozide, haloperidol, droperidol, citalopram, halofantrin, methadone, pentamidine and moxifloxacine.

- Section 4.8

The following adverse reactions should be added under the SOC Cardiac disorders with a frequency “not known”:

QT prolongation, Torsade de pointes

The following adverse reactions should be added under the SOC Psychiatric disorders with a frequency “not known”:

hallucinations, aggression

The following adverse reactions should be added under the SOC Nervous system disorders with a frequency “not known”:

neuroleptic malignant syndrome, psychomotor hyperactivity

The following adverse reactions should be added under the SOC Blood and lymphatic system disorders with a frequency “not known”:

thrombocytopenia

- Section 4.9

The recommendations for signs and symptoms of overdose should be amended as follows:

Prolonged QT interval and cases of severe arrhythmias with fatal outcome have been described in overdose of phenothiazines.

Package Leaflet

- Section 2

Warnings and precautions for use

Check with your doctor of nurse before having <Medicinal product> if:

You have any serious heart problems

You have any personal or family history of heart disease

You have an irregular heartbeat

Other medicines and *[...]*

Also tell your doctor or pharmacist if you are taking, have recently taken or might take any of the following:

medicines that can affect your heart rhythm

- Section 3

Having the medicine

If you feel burning or pain during or shortly after application, tell your doctor or nurse immediately.

- Section 4

Frequency ´not known (cannot be estimated from the available data)´:

Abnormal electrical activity of the heart that affects its rhythm, including life-threatening rhythm disturbance

A serious reaction with fever, rigid muscles, changing blood pressure and coma (neuroleptic malignant syndrome)

Low levels of blood platelets (which can lead to bleeding and bruising)

Restlessness

Hallucinations

Aggression

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 January 2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	27 March 2025