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 clozapine, the scientific conclusions are as follows:

Appendicitis

In view of available pharmacovigilance data, supported by a retrospective cohort study, the PRAC considers a causal association between clozapine and appendicitis cannot be excluded and is at least a reasonable possibility. The proposed mechanism is consistent with other gastrointestinal complications of clozapine. In view of the seriousness and consistency of the evidence, an update of sections 4.4 and 4.8 of the summary of product characteristics, as well as the corresponding sections of the package leaflet, is deemed necessary. The PRAC concluded that the product information of medicinal products containing clozapine should be amended accordingly.

Haematological malignancies

In view of cumulative evidence from epidemiological studies and a plausible biological mechanism, the PRAC considers a causal association between clozapine exposure and haematological malignancies cannot be excluded and is at least a reasonable possibility. In view of the seriousness and consistency of the evidence, an update of sections, 4.8 of the summary of product characteristics, as well as the corresponding section of the package leaflet, is deemed necessary. The PRAC concluded that the product information of products containing clozapine should be amended accordingly.

DRESS (drug reaction with eosinophilia and systemic syndrome)

In view of available data from cumulative evidence on SCARs reactions from spontaneous reports and literature and considering that a causal relationship has already been established between clozapine and DRESS, the PRAC considers a causal relationship between clozapine and DRESS is at least a reasonable possibility. The PRAC considers a warning in section 4.4 as necessary to raise awareness in HCPs and patients for an early recognition. The PRAC concluded that the product information of products containing clozapine should be amended accordingly.

Drug-drug interaction (DDI) between clozapine and valproate: potential effects on myocarditis

In view of available published data on the risk associated with drug-drug interaction with valproic acid (VPA) from literature, the PRAC considers a causal relationship is at least a reasonable possibility. Studies consistently indicate a higher incidence of ADRs with the combined use of valproic acid and clozapine and suggest that valproic acid (VPA) during clozapine initiation is a risk factor for clozapine-induced inflammation and serious adverse events such as myocarditis. The PRAC concluded that the product information of products containing clozapine 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 clozapine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing clozapine 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~~)

Appendicitis

Summary of Product Characteristics

Section 4.4 Warning and Precautions

(…)

Anticholinergic effects

<INN> exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of prostatic enlargement and narrow-angle glaucoma. Probably on account of its anticholinergic properties, <INN> has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction, paralytic ileus, **appendicitis**, megacolon and intestinal infarction ischaemia (see section 4.8). On rare occasions these cases have been fatal. Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised and actively treated.

Section 4.8

The following adverse reaction should be added under the SOC Gastrointestinal Disorders with a frequency not known (new text underlined and in bold):

Frequency not known: **Appendicitis** *, **, ***

* Adverse reactions from post-marketing experience as spontaneous reporting and case reports in literature

** Some cases have been fatal

***** Including appendicitis perforated**

Package Leaflet

Section 2 What you need to know before you take X

Warnings and precautions

Tell your doctor immediately before taking the next <Product> tablet

- **If you develop signs and symptoms of appendicitis; these may include intense and worsening abdominal pain that begins near the navel and moves to the lower right side, made worse by movement, coughing or pressing the area. Other signs can include constipation, abdominal swelling malaise, mild fever, vomiting, loss of appetite or diarrhea. You will need an urgent medical examination by your doctor.**

Section 4 Possible side effects

Some side effects can be serious and need immediate medical attention. Tell your doctor immediately before taking the next <Product> tablet if you experience any of the following:

Frequency 'not known': **inflammation of the appendix (appendicitis)**

Haematological malignancies

Summary of Product Characteristics

Section 4.8 Undesirable effects

System Organ Class: Neoplasms Benign, malignant and unspecified (incl cysts and polyps)

Frequency 'not known': **Haematological malignancy**

Description of Selected Adverse Reactions

Haematological malignancy (HM)

Epidemiological studies have shown a cumulative dose- and time-dependent association between clozapine and haematological malignancy. In a large cohort study, the absolute risk of developing a haematological malignancy was 61 cases per 100,000 person-years among clozapine-treated patients, versus 41 cases per 100,000 person-years in those receiving other antipsychotic medicines, corresponding to 0.7% in clozapine users versus 0.5% in the other group, over a mean follow-up of 12.3 years. A high cumulative clozapine exposure was associated with an adjusted odds ratio (aOR) of 3.35 (95% CI: 2.22–5.05), and treatment duration ≥5 years with an aOR of 2.94 (95% CI: 2.07–4.17). A cumulative dose–response relationship was also observed for lymphoma, with an aOR of 4.06 (95% CI: 2.60–6.33) at the same cumulative dose threshold. The extent to which haematological monitoring of clozapine-treated patients may contribute to these estimates is not known.

Package Leaflet

Section 4 Possible side effects

Frequency 'not known': **blood cancer (haematological malignancy)**

A small increased risk of developing blood cancer has been observed in patients taking clozapine, especially in cases of longer treatment.

Symptoms could include

- **unexplained fever**
- **swollen glands,**
- **persistent infections during the treatment**
- **weight loss**
- **extreme tiredness**
- **redness**
- **night sweats**
- **easy bruising or bleeding**

DRESS (drug reaction with eosinophilia and systemic syndrome)

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Severe cutaneous adverse reactions (SCARs)

Drug reaction with eosinophilia and systemic syndrome (DRESS), which can be life-threatening or fatal, have been reported in association with clozapine (see section 4.8).

Patients should be advised of the signs and symptoms of DRESS and monitored closely.

If signs and symptoms suggestive of this reaction appear, clozapine should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed DRESS with the use of clozapine, treatment with clozapine must not be restarted in this patient at any time.

Package Leaflet

Section 2- What you need to know before you take [product name]

Warnings and precautions - Take special care with [Product name]:

Talk to your doctor before taking [product name]:

If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking [product name].

This medicine can cause serious skin reactions. Stop using clozapine and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions.

Drug-drug interaction (DDI) between clozapine and valproate: potential effects on myocarditis

Summary of Product Characteristics

- Section 4.5

Concomitant treatment of clozapine and valproic acid may increase the risk of neutropenia **and clozapine-induced myocarditis**. If concomitant use of clozapine with valproic acid is necessary, careful monitoring is required.

[…]

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	05 January 2026
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 February 2026