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 quetiapine, the scientific conclusions are as follows:

In view of the available data on serotonin syndrome from 10 spontaneous cases (all after quetiapine increase or addition while using other antidepressants or antipsychotics), including in 5 cases a close temporal relationship, and in 8 cases a positive de-challenge, and in view of a plausible mechanism of action, the PRAC concludes there is a reasonable possibility of a drug-drug interaction with serotonergic drugs leading to serotonin syndrome. The PRAC concluded that the product information of products containing quetiapine 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 quetiapine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing quetiapine 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, to be placed directly following the existing Neuroleptic malignant syndrome-warning:

Serotonin syndrome

Concomitant administration of [product name] and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

- Section 4.5

An interaction should be added as follows, to be placed directly following the existing interaction warning that quetiapine should be used with caution in combination with other centrally acting medicinal products:

Quetiapine should be used with caution in combination with serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Package Leaflet

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

Warnings and precautions

Talk to your doctor or pharmacist before taking [product name]:

- **If you have depression or other conditions that are treated with antidepressants. The use of these medicines together with [product name] can lead to serotonin syndrome, a potentially life-threatening condition (see "Other medicines and [product name]").**

Other medicines and [product name]
[…]
Tell your doctor if you are taking any of the following medicines:

- **anti-depressants. These medicines may interact with [product name] and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, hallucinations, coma, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C (serotonin syndrome). Contact your doctor when experiencing such symptoms.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	05/05/2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	04/07/2024