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:

Literature search performed by the brand leader AstraZeneca, has identified a publication *(Taylor and Graudins et al.: Extended-release (XR) quetiapine overdose is associated with delayed development of peak toxicity and prolonged recovery when compared to immediate-release (IR) quetiapine overdose: a retrospective cohort study. Clinical Toxicology 2017;5:460)* which showed delayed peak sedation, delayed recovery from sedation and longer duration of intubation for overdose with XR quetiapine compared with IR quetiapine. This effect disappeared when patients were included who also had ingested other sedating drugs.

Median time to lowest Glasgow Coma Scale (GCS) was longer for XR (7 hours [IQR 4.9-11] versus 3.8 hours [IQR 2.4-5.7], $p<0.001$). Median time to peak pulse was greater for XR (9 hours [IQR 3-12] versus 2.5 hours [IQR 1.5-5], $p=0.01$). Median time to recovery from sedation was longer for XR (20 hours [IQR 12-39] versus 12 hours [IQR 5.5-22], $p<0.05$). Median intubation duration was longer for XR, (47 hours versus 17 hours, $p=0.04$). The ingested doses for quetiapine XR was higher than for quetiapine IR but the degree of sedation and tachycardia was similar for XR and IR quetiapine overdoses. Delayed absorption and reduced peak serum concentrations following XR ingestions may explain this.

Therefore, this information should be reflected in section 4.9 ‘Overdose’ of quetiapine XR product informations.

Also, the LMS identified an article by (*Raquber-Luthy et al.: Gastric pharmacobezoars in quetiapine extended-release overdose: a case series, Clin Toxicol (Phila). 2013 Dec;51(10):937-40))* which included six cases of overdose with quetiapine XR with bezoar formation. In these cases gastroscopic pharmacobezoar removal was achieved without complications in all patients, but was difficult due to the particular "gelatinous-sticky-pasty" consistency of the concretion. The authors concluded the possibility of pharmacobezoar formation following a quetiapine XR overdose should be considered, as this may influence acute patient management.

The LMS considers that this information should be reflected in section 4.9 ‘Overdose’ of quetiapine XR product information. Based on comments by concerned member states, the recommendations for the SmPC have been adjusted.

In addition, after the data lock point of 31 July 2017, the brand leader MAH validated a safety signal for Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) which led to the request for a cumulative review in the PAR. Based on the review, the LMS proposes to add DRESS to section 4.8 of the SPC and section 4 of the PL. The MAH’s search yielded a total of 19 cases including 1 from a pediatric clinical trial and 5 from literature. Two of these cases concerned Pseudolymphoma and were not further reviewed. Some cases could be excluded since more plausible explanations were identified (e.g. concomitant medication) or diagnosis not compatible with DRESS. Based on assessment of this review 3 key cases of DRESS were identified that suggest a possible causal relationship with quetiapine for DRESS. All three cases reported positive dechallenge (quetiapine) and in one case a positive rechallenge with quetiapine was reported. The SmPC of quetiapine already includes information concerning SCAR, but not DRESS. DRESS maybe related to quetiapine with at least reasonable plausibility and this information should be reflected in section 4.8 Undesirable effects of the SmPC.

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 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 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 quetiapine are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that 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)

The following changes to the product information of medicinal products containing the active substance quetiapine and quetiapine **XR** are recommended (new text **underlined and in bold**, deleted text ~~strike-through~~):

Summary of Product Characteristics

- Section 4.8

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with quetiapine treatment

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

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome). Stop using <quetiapine> if you develop these symptoms and contact your doctor or seek medical attention immediately

The following changes to the product information of medicinal products containing Quetiapine **XR only** are recommended (new text **underlined and in bold**, deleted text ~~strike-through~~):

Summary of Product Characteristics

- Section 4.9 Overdose

A text should be added as follows:

[..}

"In case of overdose with extended-release quetiapine there is a delayed peak sedation and peak pulse and prolonged recovery compared with IR Quetiapine overdose."

"In case of a quetiapine extended-release overdose gastric bezoar formation has been reported and appropriate diagnostic imaging is recommended to further guide patient management.

Endoscopic pharmacobezoar removal has been performed successfully in some cases".

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	April 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	9 June 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	8 August 2018