Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation

Scientific conclusions

Overall summary of the scientific evaluation of Seroquel/Seroquel XR and associated names (see Annex I)

Quetiapine is an atypical antipsychotic agent, which together with its active metabolite – norquetiapine – interacts with a broad range of neurotransmitter receptors including serotonin 5-hydroxytryptophan type 2 (5HT2A), dopamine type 1 and type 2 (D1, D2), histamine and adrenergic receptors (greatly α1). The active metabolite, noraquetapine, shows greater affinity for 5HT2A receptor and is an inhibitor of the norepinephrine transporter.

The exact mechanism of action of quetiapine, similarly with other antipsychotics, is still unknown, but the combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2 receptors may contribute to its psychotropic activity and mood stabilizing properties.

Seroquel (quetiapine) and Seroquel XR (quetiapine prolonged released formulation) are used for the treatment of schizophrenia and bipolar disorder, being Seroquel XR also used as an add-on treatment in major depression.

Seroquel was first approved in the United Kingdom July 1997 and is available in 25 mg, 100 mg, 150 mg, 200 mg and 300 mg as immediate released tablets. Seroquel XR or XL was first approved in the United States in May 2007 and it is available in 50 mg, 150 mg, 200 mg and 400 mg, and as prolonged released tablets in all European Union (EU) Member States (MS), with exception of Bulgaria and Poland. It is approved via national, mutual recognition (MRP) or decentralised procedures (DCP).

Due to the combination of the MRP/DCP and national granted MAs some divergent information has been identified in the product information (PI) for Seroquel and Seroquel XR. Hence, these medicinal products were included in the list of products for PI harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC. Due to the divergent national decisions taken by MS concerning the authorisation of the above-mentioned products (and its associated names), the European Commission notified the CHMP/EMA Secretariat of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised PIs and thus to harmonise its divergent PIs across the EU.

The CHMP addressed a list of questions to the MAH, pointing out the sections of the products SmPC where divergences existed. The SmPC harmonisation considered all relevant therapeutic and regulatory guidelines in the EU. The proposal presented by the MAH reflected the latest scientific information.

It is hereafter summarised the main points discussed for the harmonisation of the different sections of the SmPC.

Section 4.1 – Therapeutic Indications

Seroquel and Seroquel XR are indicated for treatment of schizophrenia and bipolar disorder. Seroquel XR is indicated as well as an add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy.

- *treatment of schizophrenia*

From all the EU MSs in which Seroquel is approved, only one had a different wording from the MRP-approved SmPC by having the following additional text: “treatment of acute and chronic psychosis, including schizophrenia and manic episodes associated with bipolar disorder”. The CHMP supported the MAH decision that the harmonised wording for this indication would be aligned with the MRP-approved SmPC text i.e. separating the indications “Schizophrenia” and “Manic episodes in bipolar disorder”. The treatment of acute and chronic psychosis is a broader indication than schizophrenia and

as such should be substantiated adequately. A simple extrapolation from schizophrenia trials to other psychosis is not encouraged by the Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia (EMA/CHMP/40072/2010 Rev. 1). Therefore the harmonised wording for this indication is "Treatment of schizophrenia".

Seroquel XR wording was disharmonised by one MS in which the following text: "Treatment of Schizophrenia, including preventing relapse in stable schizophrenic patients who have been maintained on Seroquel XR" was omitted in comparison with the MRP SmPC. The CHMP agreed that the wording was not acceptable to be included in the harmonised text, since prevention of relapse is considered to be part of good clinical practise in the treatment of schizophrenia and as such not required to be clearly specified in the therapeutic indication section of the SmPC. The harmonised wording for this indication is "Treatment of schizophrenia".

- *treatment of bipolar disorder*
    - *for the treatment of moderate to severe manic episodes in bipolar disorder*

In four MSs the wording "moderate to severe" was missing in the therapeutic indication. The pivotal clinical studies for this indication were conducted in a patient population having moderate to severe manic episodes in bipolar disorder. The harmonised wording for the SmPC and found in the majority of the EU MSs i.e. "moderate to severe" is considered appropriate and provides useful information for the prescribing physician as to the patient population that will benefit from taking Seroquel.

    - *for the treatment of major depressive episodes in bipolar disorder*

The indication "major depressive episodes" in the MRP SmPC was approved on November 2008 when the indication for bipolar depression was first approved. However, divergent wording has been identified in seven MSs in which "major" was missing in the indication. Therefore, the agreed harmonised text is "for the treatment of major depressive episodes in bipolar disorder".

    - *for the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment.*

Three MSs had the following wording: "For the prevention of recurrence in patients with bipolar disorder, in patients whose manic, mixed or depressive episode has responded to quetiapine treatment", while twenty other MSs had the current MRP-approved SmPC, without the word "mixed".

The limited available data on treatment of mixed episodes was not designed to investigate the efficacy/safety of quetiapine in mixed episodes and showed only a positive non-significant trend in this subgroup. Therefore, the agreed harmonised text is "*for the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment*".

Section 4.2 – Posology and method of administration

In several MSs there were discrepancies in section 4.2 due to the differences in the indications. Furthermore, the recommendations for up-titration and for daily dose in some indications i.e. schizophrenia, moderate to severe episodes in bipolar disorder and major depressive episodes in bipolar disorder differed among MSs. There were also discrepancies regarding recommendations for special population groups namely elderly and paediatric, administration with/without food.

All divergences have been identified and it was agreed that the harmonised text would be aligned with the wording of the MRP SmPC for Seroquel and Seroquel XR. Please see SmPC for Seroquel and for Seroquel XR in Annex III.

Section 4.4 – Special warnings and precautions for use

Metabolic risk

The information in this section was mainly consistent in the SmPC of Seroquel and Seroquel XR across all MSs. However, the CHMP recommended moving this warning to a more prominent place in this section in order to increase awareness to the risk of developing metabolic syndrome associated with quetiapine treatment.

Moreover, the CHMP requested further amendments to this section to include information on the need to conduct screening of metabolic parameters i.e. weight, glucose and lipids prior to treatment initiation and regularly during therapy. Please see SmPC for Seroquel and for Seroquel XR in Annex III.

Somnolence and dizziness

In two MSs the heading read "Somnolence" instead of "Somnolence and dizziness". This has now been harmonised. The CHMP agreed that this warning included redundant information regarding orthostatic hypotension and related dizziness, since it repeated information already included under subheading on Cardiovascular (now Orthostatic hypotension). The content was therefore reworded and harmonised across all MSs. Please see SmPC for Seroquel and for Seroquel XR in Annex III.

Orthostatic hypotension

The information in this section was mainly consistent in the SmPC of Seroquel and Seroquel XR across all MSs. However, part of the information in this section has been moved from the heading "Somnolence" as explained above. The warning concerning cardiovascular were agreed to be now under this heading i.e. "orthostatic hypotension" which has been re-named. Although there were no major divergences in the wording, a more concise text concerning cardiovascular to prevent redundancy was agreed aiming specific product information for the prescriber instead of common knowledge on symptoms and consequences of orthostatic hypotension. Please see SmPC for Seroquel and for Seroquel XR in Annex III.

Severe neutropenia and agranulocytosis

The information in this section was mainly consistent in the SmPC across the MSs. Nevertheless, it was considered that the information on the risk of agranulocytosis was unclear. Therefore this warning was reworded to clearly state that patients need to immediately report the appearance of symptoms consistent with agranulocitosys or infection, during Seroquel therapy and physicians to proceed to white blood cells (WBC) count and absolute neutrophil count (ANC) in the absence of predisposition factors.

In addition, the MAH reviewed data concerning this risk and confirmed no fatal cases of agranulocytosis in the clinical trial data set. However, and since there were fatal post-marketing reports of agranulocytosis the harmonised wording reflects this information.

Redundant text related to resolution of leucopenia and/or neutropenia following cessation of quetiapine treatment because recovery is implied later in the same paragraph i.e. "Patients should be observed for signs and symptoms of infection and neutrophil counts followed until they exceed 1.5 X 109/l" was removed.

Lastly, an administrative change has been made to the section heading, and the frequency of severe neutropenia has been changed to maintain consistency with the information currently contained in Section 5.1 of the SmPC. Please see SmPC for Seroquel and for Seroquel XR in Annex III.

Cardiomyopathy and Myocarditis

The warning on cardiomyopathy and myocarditis was included through a type II variation, which was finalised during the assessment of this referral procedure under Article 30 from Directive 2001/83/EC started. The wording approved by the variation as follows: "*Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience, however, a causal relationship to quetiapine has not been established. Treatment with quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis".* Please see SmPC for Seroquel and for Seroquel XR in Annex III.

Hepatic Effects

Only one MS had a warning regarding the hepatic effects. The warning stated that *"If jaundice develops, quetiapine should be discontinued".* The SmPC in other MSs does not include this information.

Jaundice is a listed, rare adverse event with quetiapine (in section 4.8 of the SmPC). Discontinuing antipsychotic medication in stabilised patients is of particular concern, as well as the development of jaundice. The MAH proposal for harmonisation did not support this warning. Considering that the MAH had already committed to submit a cumulative review on hepatic effects within the PSUR in September 2014, the CHMP agreed that a harmonised wording in regard of hepatic effects should be assessed and agreed upon in the upcoming PSUR.

Constipation and intestinal obstruction

The wording on "Constipation and intestinal obstruction" was already harmonised. However, the CHMP requested this warning to be further strengthened with regards the need to manage patients with intestinal obstruction / ileus with close monitoring and urgent care to be added. Therefore, the following wording was added "*Patients with intestinal obstruction / ileus should be managed with close monitoring and urgent care".* Please see SmPC for Seroquel and for Seroquel XR in Annex III.

Other warnings of this section i.e. Extrapyramidal symptoms, Tardive Dyskinesia, Seizures, Interactions, Weight, Hyperglycaemia, Elderly patients with dementia-related psychosis and Dysphagia were also harmonised for minor divergences identified among the SmPC approved in the several MSs. Please see SmPC for Seroquel and Seroquel XR in Annex III.

Section 4.5 – Interaction with other medicinal products and other forms of interaction

After a comparison of current section 4.5 Seroquel and Seroquel XR SmPCs approved nationally versus the most recent MRP-approved Seroquel and Seroquel XR SmPC, only few divergences were noted. Mainly these regard missing information on children and adolescents who received valproate, quetiapine or both, and found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups. It was agreed that the harmonised wording related to section 4.5 is the already approved Seroquel and Seroquel XR MRP SmPC. Please see SmPC for Seroquel and Seroquel XR in Annex III.

Section 4.6 – Fertility, pregnancy and lactation

At the start of this procedure, the wording on section 4.6 was under evaluation in an MRP type II variation. The wording under review in the variation procedure was provided within the MAH responses to the CHMP list of questions of this Article 30 harmonisation procedure.

The proposed wording was in line with the current guidance and a clear distinction could be made between the data relevant for the first trimester (potential for congenital abnormalities) and the third trimester (neonatal withdrawal effects). Discussions held were mainly around the amount of data currently available for the first trimester.

Several clinical studies have been published during recent years (e.g. Haberman et al 2013) indicating that there is no major teratogenic risk due to the use of atypical antipsychotics. Common sources (Briggs et al., 2011; Reprotox Database) reviewed several case reports and some publications reporting on a limited series of pregnancies. The CHMP considered all available data which concerned more than 300 cases of exposure during pregnancy. The limited available data does not indicate a risk for congenital abnormalities. The CHMP agreed that no definitive conclusion on the risk during pregnancy can be drawn based on the data available. The final text was agreed within this harmonisation procedure and took into account the guidance provided in the guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005), which mentions the available data and lack of teratogenic effects up to now, but also states that no conclusions on risk can be drawn.

Studies in animals as explained in section 5.3 of the SmPC have shown reproductive toxicity.

In the heading referring to breastfeeding is stated that the degree of excretion in milk is not consistent. No literature review to underpin that conclusion was provided. It is known that excretion in milk is low. Generally the infant dose stays below 0.5% of the maternal dose, often even lower. However, the available data are very limited, and therefore it is recommended that a decision must be made whether to discontinue breast-feeding or to discontinue Seroquel therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the mother.

The fact that quetiapine has not been studied on human fertility is now harmonised under this subheading. Please see SmPC for Seroquel and Seroquel XR in Annex III.

Section 4.8 – Undesirable effects

This section was updated in format of the adverse reactions listed according to the QRD template. This section was also further amended to reflect the information already included in the package leaflet that exacerbation of pre-existing diabetes may occur. The final harmonised wording addresses all the identified discrepancies e.g. differences in frequency of reported adverse events like rhinitis. Please see SmPC for Seroquel and Seroquel XR in Annex III.

Section 4.9 – Overdose

At the start of this procedure, the wording on section 4.9 was under evaluation in an MRP type II variation. The wording under review was provided within the MAH responses to the CHMP list of questions of this Article 30 harmonisation procedure.

The CHMP had the opportunity to provide comments namely, the CHMP requested the MAH to remove information regarding fatal dose as this is not in line with the SmPC guideline. The proposed, harmonised text more accurately reflects the current data and knowledge on Seroquel and Seroquel XR. Please see SmPC for Seroquel and Seroquel XR in Annex III.

Section 5.1 – Pharmacodynamic properties

At the start of this procedure, the wording on this section was under evaluation in an MRP type II variation. The wording under review was provided within the MAH responses to the CHMP list of questions of this Article 30 harmonisation procedure.

The CHMP commented on the wording namely on the affinity for serotonin 5HT1A and for norepinephrine transporter (NET) due to the current limited available data in this regard. The final agreed wording is part of the harmonised SmPCs for Seroquel and for Seroquel XR. Please see Annex III.

Section 5.2 – Pharmacokinetic properties

All MSs have the same or similar wording in their Seroquel and Seroquel XR SmPCs with regards absorption, distribution, elimination, gender, elderly and renal impairment. Divergent information was identified in one MS namely with regards to hepatic impairment and paediatric population. The MAH proposed the harmonised text as per MRP SmPC which reflects the current knowledge and data on Seroquel and Seroquel XR. The proposed wording was fully endorsed by the CHMP. Please see SmPC for Seroquel and Seroquel XR in Annex III.

Section 5.3 – Preclinical safety data

All MSs have the same or similar wording in their Seroquel and Seroquel XR SmPCs with regards to preclinical safety data. However, the CHMP considered the sentence regarding the need to consider balance on the benefits and risk of quetiapine to be redundant and was therefore agreed to be removed. Further amendments were introduced in this section consequently to the modifications made in section 4.6. Please see SmPC for Seroquel and Seroquel XR in Annex III.

Package Leaflet (PL)

Following all the changes in the SmPC there were amendments made to the Package Leaflet. The final PL wording was agreed by the CHMP. Please see Product Information for Seroquel and for Seroquel XR and associated names in Annex III.

QUALITY – MODULE 3

The MAH submitted a proposal for harmonisation of the Quality module. As a result of this harmonisation procedure, Module 3 was updated to harmonise the information between the Member States. The manufacture and control of both the active substance and the finished product comply with CHMP/ICH guidelines. Quality of the product is considered satisfactory.

Based on the review of data the CHMP adopted a harmonised Module 3.

Grounds for the variation to the terms of the marketing authorisation(s)

In conclusion, based on the assessment of the MAH proposal and responses and following the discussions of the committee, the CHMP adopted harmonised sets of Product Information documents of Seroquel/Seroquel XR and associated names.

A harmonised Module 3 was also adopted. Based on the above, the CHMP considers the benefit/risk ratio of Seroquel/Seroquel XR and associated names to be favourable and the harmonised Product Information documents to be approvable

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC
- The committee considered the identified divergences for the Seroquel and Seroquel XR and associated names regarding the therapeutic indications, posology and method of administration, special warnings and precautions for use, as well as in the remaining sections of the SmPCs
- The committee reviewed the data submitted by the MAH on the existing clinical studies, the pharmacovigilance data and the published literature justifying the proposed harmonisation of the product information
- The committee agreed the harmonisation of the summary of product characteristics, labelling and package leaflets proposed by the marketing authorisation holder.

the CHMP has recommended the variation to the terms of the marketing authorisations for which the summary of product characteristics, labelling and package leaflets are set out in Annex III for Seroquel and Seroquel XR and associated names (see Annex I).