06 August 2014
EMA/CHMP/489245/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pursuant to Article 30 of Directive 2001/83/EC

Seroquel/Seroquel XR and associated names

International Non-proprietary Name: quetiapine

Procedure no: EMEA/H/A-30/1362

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 12 June 2013 the European Commission presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products:

Seroquel and Seroquel XR and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the June, 2013 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Zwieten-Boot (NL) as rapporteur and Agnes Gyurasics (HU) as co-rapporteur. In October 2013 the (co)-rapporteurship was transferred to Hans Hillege and Melinda Sobor, respectively.

Seroquel medicinal products are approved in all Members States (MS), including Iceland and Norway, except in Bulgaria, Czech Republic, France, Hungary, Poland and Slovakia.

Seroquel XR medicinal products are approved in all MSs, including Iceland and Norway except in Bulgaria and Poland.

2. Scientific discussion during the referral procedure

2.1. Introduction

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 EU MSs, with exception of Bulgaria and Poland. It is approved via national, mutual recognition or decentralised procedures.

Due to divergent national decisions taken by MSs, Seroquel and Seroquel XR and associated names were included in the list of products for Summary of Product Characteristics (SmPC) harmonisation, requested by the Coordination Group for Mutual Recognition and Decentralized Procedures - Human (CMDh). The European Commission notified the European Medicines Agency/ Committee for Medicinal

Products for Human Use (EMA/CHMP) secretariat of an official referral under Article 30 of Directive 2001/83/EC to resolve the divergences amongst the nationally authorised Seroquel and Seroquel XR across the MS. A pre-referral meeting between the EMA and marketing authorisation holder (MAH) was held on 14 March 2013. The CHMP addressed a list of questions to the MAH, pointing out the sections of the products SmPC where divergences existed.

2.2. Critical Evaluation

This report was written taking in to account all the sections where divergences were found. All the section that are not clearly mentioned hereafter, the wording was already harmonised.

2.2.1. Quality aspects

Introduction

AstraZeneca group of companies and associated companies took the opportunity to harmonise the Quality dossier for Seroquel/ Seroquel XR and associated names as part of this Article 30 referral procedure.

The harmonised dossier was provided for the active substance (quetiapine) and finished product.

Active Substance

The MAH took the opportunity to harmonise the active substance supply chain across all member states, additional information on the milling of the active substance was provided, re-formatting of the starting materials section to identify contributory reagents, including an additional benzene specification for toluene (NMT 500 ppm). The MAH also took the opportunity to include additional information in the characterisation section on elucidation of ArP, Des Etanol and N-oxide.

The limits of the following specifications: water content, related substances (other individual, total others, total of all related substances), related solvents are harmonised. The analytical procedure for N-methylpyrrolidone has been included as a result of the change to specification and the analytical procedure. Additional information was provided in the 'Validation Report for Related Substances by HPLC', namely updates to the robustness section including information on the effects of flow rate, temperature, pH and mobile phase. Recent batch analysis was presented. The data presented is reported to the proposed harmonised specification. A justification for the acceptance criteria for the tests outlined in the revised specification was presented.

For the 50, 200, 300, 400 mg strengths the information was updated to clarify that the reference standard selected complied with the specification in place at the time of testing.

In relation to the container closure system, the information has been updated to include an additional clause 'The liners comply with the European Pharmacopoeia monograph, 3.1.4', 'Polyethylene without additives for containers for parenteral preparations and for ophthalmic preparations.'

The primary stability data provided is approved in all other member states. Recent commercial stability data has been provided in the harmonized dossier. Section 3.2.S.7.2 was not included in the original marketing authorisation application but has been created for completeness to describe the annual maintenance testing protocol. A retest re-test period of 3 years is still justified based on the current stability results. The storage condition is: store below 30°C.

Finished product

The MAH took the opportunity to harmonise the submitted extended release finished product information in relation to description and composition, pharmaceutical development, manufacture, control of excipients, specifications, reference standard materials, and stability.

The MAH also took the opportunity to harmonise the submitted immediate release finished product information in relation to description and composition, pharmaceutical development, manufacture, control of excipients, specifications of the finished product, analytical methods and method validations, reference standards, container closure system and stability.

Discussion and Conclusions on quality

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.

2.2.2. Clinical aspects

The proposal presented by the MAH reflected the latest scientific information aligned with the product information authorised via mutual recognition procedure (MRP).

It is hereafter summarised the main points discussed for the harmonisation of the different sections of the Summary of Product Characteristics (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 divergent in 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. These studies were:

- IL/0104 – An International, Multicenter, Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of Seroquel and Haloperidol as Monotherapy in the Treatment of Acute Mania;
- IL/0105 - An International, Multicenter, Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of Seroquel and Lithium as Monotherapy in the Treatment of Acute Mania;
- IL/0099 - A Multicenter, Doubie-blind, Randomized, Placebo controlled Trial of the Safety and Efficacy of Seroquel as Add-on Therapy with Lithium or Divalproex in the Treatment of Acute Mania;
- IL/0100 - An international, Multicenter, Double-blind, Randomized, Placebo-controiled Study of the Safety and Efficacy of Seroquel as Add-on Therapy with Lithium or Divalproex in the Treatment of Acute Mania.

The wording "moderate to severe" is based on an YMRS score of at least 20 and a score of at least 4 on at least 2 of the core YMRS items of Irritability, Speech, Content and Disruptive/Aggressive behaviours. In addition, patients had to have a score of at least 4 on the CGI-BP Severity of Illness.

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.

The MAH proposed to modify the text "for the treatment of major depressive episodes in bipolar disorder" to "for the treatment of major depressive episodes associated with bipolar disorder". The CHMP considered that the inclusion of the text "associated with" instead of "in" was less stringent than the current wording. 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 MAH proposal for the harmonised wording to include the word "mixed" was based on the fact that the patient populations studied were selected in concordance with CHMP Note for guidance on clinical investigation of medicinal products for the treatment and prevention of Bipolar Disorder (CPMP/EWP/567/98) and did include individuals with manic, depressed or mixed episodes.

The CHMP did not support this proposal since the short term treatment of mixed episodes has not been demonstrated. Data on treatment of mixed episodes provided by the MAH in this submission, was not designed to investigate the efficacy/safety of Seroquel in mixed episodes and only a positive non-significant trend has been observed, in this subgroup. It is therefore information not included in any of the product information approved in MS hence not subject to harmonisation.

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 the recommended daily dose in some indications differed in some of the MSs. There were also discrepancies among MSs on existing recommendations for special population groups.

Dosing Schedule

The general introductory guidance in this section is now harmonised and aligned with the MRP SmPC to reminder physicians to give clear information to patients. The information on the administration of quetiapine with food was also harmonised and is aligned with MRP-approved SmPC which recommends administration with or without food for Seroquel and without food for Seroquel XR.

For the treatment of schizophrenia

All except one MS, recommend the same dose titration i.e. dose range of 300 to 450 mg/ day from Day 4 onwards for the treatment of Schizophrenia. This information is now harmonised in all MS.

For the treatment of moderate to severe episodes in bipolar disorder

Most MSs have the same wording or essentially the same of the MRP SmPC for Seroquel with regards the dosing regimen for Day1-4 and up to Day 6 in this indication. Two MSs have additional text "As monotherapy or as adjunct therapy to mood stabilisers".

The MAH proposal to include reference to "monotherapy or as an adjunct therapy to mood stabilizers" in section 4.2 was not agreed by CHMP. The CHMP considered that the information regarding add-on therapy to section 4.2 was not supported based on results of the a post-authorisation commitment (PAC) study which showed moderate efficacy of adding lithium to Seroquel and considerable increased safety concerns including higher rates of tremor, somnolence, dizziness, diarrhoea, vomiting, extrapyramidal symptoms (EPS), and weight gain. The results of the study are described in section 5.1 of the SmPC but these results and the benefit/risk were not considered justifying mentioning in section 4.2. Therefore this sentence is not part of the harmonised text.

For the treatment of major depressive episodes in bipolar disorder

Most MSs have the same wording or essentially the same of the MRP SmPC for Seroquel and for Seroquel XR with regards the dosing regimen in this indication.

Divergences were found in few MSs and mainly relate to an extended recommendation for Seroquel to be taken at bedtime, potential for dose increased to 400mg on day 5 and 600mg on Day 8 if necessary and missing guidance in case of doses higher than 300 mg should be initiated by physicians experienced in treating bipolar disorder.

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 Seroquel XR in Annex III.

Elderly

In the majority of the MSs the information in this section was essentially the same in the SmPC and identical to the MRP-approved SmPC text. However, in two MSs the SmPCs had specific dosing instructions for "elderly patients to start on Seroquel 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg, to an effective dose". The MRP-approved SmPC text will be the harmonised SmPC text as it enables the prescribing physician to determine the most appropriate starting dose of Seroquel for elderly patients. Therefore the final harmonised wording is the one of the MRP-SmPC which can be found in Annex III.

Paediatric population

In all except one MS the information on was consistent. Divergence was found in one MS in which the SmPC made reference to the clinical studies available in this population. The harmonised SmPC wording reads as follows "*The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1 and 5.2*", which is aligned with the MRP SmPC.

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 section 4.4, i.e. right under the warning regarding suicide, 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 Seroquel XR in Annex III.

Extrapyramidal symptoms (EPS)

The Seroquel SmPC approved in two MSs, missed information on development of akathisia. This has now been harmonised in all MSs, please see SmPC for Seroquel in Annex III.

Regarding Seroquel XR, one MS had combined information on EPS and tardive dyskinesia under the same heading and had slightly different wording. The harmonised SmPC for Seroquel XR has the mentioned subsections separated. Please see SmPC for Seroquel XR in Annex III.

Tardive dyskinesia

This warning was harmonised in majority of the MSs. However, in one MS the warning on tardive dyskinesia was missing. The wording is going to be in the Seroquel SmPC in all MSs.

As mentioned above, the wording regarding extrapyramidal symptoms and tardive dyskinesia will be separate in the harmonised Seroquel XR SmPC. Please see SmPC for Seroquel and 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 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 Seroquel XR in Annex III.

Seizures

Currently there is no data available about the incidence of seizures in patients receiving quetiapine and with history of seizures disorders. This information has now been harmonised in the SmPC. Please see SmPC for Seroquel and 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 quetiapine 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 Seroquel XR in Annex III.

Interactions

All MSs have the same wording in their Seroquel and Seroquel XR SmPCs, respectively, except one MS in which the SmPC for Seroquel provides examples of potent CYP3A4 inhibitors e.g. azole antifungals,

macrolide antibiotics and HIV protease inhibitors, but misses information when used with an non-inducer e.g. sodium valproate.

The wording has now been harmonised in line with the majority of EU MSs. Please see SmPC for Seroquel and Seroquel XR in Annex III.

Weight

All MSs have the same or similar wording in their Seroquel and Seroquel XR SmPCs, except one MS in which is missing the wording on utilising antipsychotic guidelines, and has additional wording regarding discontinuation of treatment. The MAH proposal for harmonised text aligned with MRP- SmPC was agreed by CHMP. Please see SmPC for Seroquel and Seroquel XR in Annex III.

Hyperglycaemia

All except one MS had the same wording regarding hyperglycaemia in their Seroquel and Seroquel XR SmPCs. In this MS the information on the risk of hyperglycaemia and information on diabetes was incomplete. The harmonised wording is aligned with the majority of the MSs. Please see SmPC for Seroquel and 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 Seroquel XR in Annex III.

Elderly patients with dementia-related psychosis

All except one MS had divergent information in this section of the SmPC. This section is now harmonised and aligned with the MRP-approved SmPC which provides adequate information for managing elderly patients with dementia-related psychosis. Please see SmPC for Seroquel and 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 did not included 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.

Dysphagia

The vast majority of the MSs had harmonised information that quetiapine should be used with caution in patients at risk for aspiration pneumonia since dysphagia has been reported with quetiapine. Only one MS had a different heading text "Dysphagia and Aspiration" and different wording in the Seroquel XR SmPC. The MRP-approved text on "Dysphagia" is agreed to be the harmonised text across MSs**.** Please see SmPC for Seroquel and Seroquel XR in Annex III.

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 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 in 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 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 quetiapine 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

In section 4.8, the MAH was requested to update the format of the adverse reactions list 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 in 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 quetiapine. Please see SmPC for Seroquel and Seroquel XR in Annex III.

Section 5.1 – Pharmacodynamic properties

At the start of this procedure, the wording in 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.

Labelling and Package Leaflet

Harmonised versions of the labelling and of the package leaflet were adopted. The changes to the SmPC, when relevant, were also reflected in the package leaflet. Please see Product information for Seroquel and Seroquel XR in Annex III.

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

In conclusion, the CHMP recommended the revision and harmonisation of the Product Information for Seroquel/Seroquel XR and adopted the following harmonised indications:

Seroquel/Seroquel XR is indicated for the:

- *treatment of Schizophrenia*
- *treatment of bipolar disorder:*
    - *For the treatment of moderate to severe manic episodes in bipolar disorder*
    - *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.*

In addition, Seroquel XR is also indicated as

- *add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy.*

2.5. Conclusions

The basis for this referral procedure was a harmonisation of the SmPC, labelling and package leaflet.

The CHMP having considered:

- the rapporteur and co-rapporteur assessment reports,
- scientific discussion within the Committee,
- comments and commitments from the marketing authorisation holder,

A harmonised Module 3 was also adopted.

the CHMP was of the opinion that the benefit/risk ratio of Seroquel and Seroquel XR and associated names is considered to be favourable. The CHMP adopted a positive opinion recommending the harmonisation of the SmPC, labelling and package leaflet as set out in Annex III of the CHMP opinion for Seroquel and Seroquel XR and associated names (see Annex I).