CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Seroquel XR 150 mg, prolonged release tablets AstraZeneca B.V., the Netherlands

quetiapine fumarate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0156/012/DC
Registration number in the Netherlands: RVG 102408

17 March 2010

Pharmacotherapeutic group:	antipsychotics; diazepines, oxazepines and thiazepines
ATC code:	N05AH04
Route of administration:	oral
Therapeutic indication:	schizophrenia and prevention of relapse in stable schizophrenic patients; moderate to severe manic episodes; major depressive episodes
Prescription status:	prescription only
Date of authorisation in NL:	17 December 2008
Concerned Member States:	Decentralised procedure with AT, BE, CY, DE, DK, EL, ES, FI, IE, IS, LU, MT, NO, PL, PT, SE
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Seroquel XR 150 mg, prolonged release tablets, from AstraZeneca B.V. The date of authorisation was on 17 December 2008 in the Netherlands.

The product is indicated for treatment of:

- schizophrenia,
    - including preventing relapse in stable schizophrenic patients who have been maintained on Seroquel XR.
- Seroquel XR is indicated for the 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 in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment.

A comprehensive description of the indications and posology is given in the SPC. The indication 'prevention of recurrence in patients with bipolar disorder' has been approved via variation NL/H/0156/012/II/057, which is discussed briefly in Annex I.

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1- and D_2- receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine. Additionally, N-desalkyl quetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic a_1 receptors, with a lower affinity at adrenergic a_2 and serotonin $5HT_1A$ receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

This decentralised procedure concerns an application made according to article 8.3 of Directive 2001/83/EC. The Seroquel XR 150 mg, prolonged release tablets are a line extension, a different strength, to the already existing Seroquel XR 50, 200, 300 and 400 mg tablets, which have been authorised via MRP procedure NL/H/0156/08-011/MR. Seroquel XR 50, 200, 300 and 400 mg tablets were submitted as a line extension as well, but as a different pharmaceutical form to Seroquel immediate release tablets, which have been authorised via MRP procedure NL/H/0156/01-07/MR. Seroquel IR tablets have been registered since 27 April 1998 in the Netherlands.

One could argue that Seroquel XR 150 mg should be considered a line extension to Seroquel IR also. However, since the dossier for Seroquel XR 50, 200, 300 and 400 mg (NL/H/0156/08-011) also contained new studies performed with the XR formulation, it was found acceptable to submit the current application as a line extension to the already approved XR tablets. The additional strength of 150 mg tablets complements the existing strengths of Seroquel XR and will give physicians greater dose flexibility.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This application is a line extension of the dossier presented for procedure NL/H/0156/08-011/MR. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the authorised Seroquel XR tablets. To this end the MAH has submitted dissolution data and an IVIV-C (in-vitro-in-vivo correlation) model.

No additional non-clinical data have been submitted, which is acceptable for this kind of application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is quetiapine fumarate, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.*) or any other pharmacopoeia. The active substance is a white to off-white crystalline non-hygroscopic powder that is soluble in dilute acidic and basic solutions, slightly soluble in acetone, ethanol and methanol, and very slightly soluble in ether. Quetiapine is present as quetiapine fumarate and consists of two units quetiapine and one unit fumaric acid. Quetiapine fumarate does not exhibit polymorphism.

Control of drug substance
The active substance specification is considered adequate to control the quality. The substance is tested for appearance, water content, sulphated ash, strength, related substances, residual solvents, heavy metals, identification and specific surface area. Batch analytical data demonstrating compliance with this specification have been provided for 29 commercial scale production batches.

Stability of drug substance
Stability data on the active substance have been provided for 7 batches during storage at 25 ºC/60% RH and 40 ºC/75% RH in accordance with applicable European guidelines. The solid substance is stable with respect to degradation, temperature and light. Based on the data provided, the re-test period of 3 years could be granted. The additional storage condition *'store below 30 ºC'* is not necessary, but acceptable.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Seroquel XR 150 mg contains as active substance 150 mg of quetiapine as quetiapine fumarate, and is formulated as a white tablet engraved with "XR 150" on one side.

The prolonged release tablets are packed in PVC+PCTFE blisters with aluminium backing. The blisters are packaged in a cardboard box.

The excipients are:
Core - microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose.
Coating - hypromellose, macrogol, titanium dioxide (E171).

Pharmaceutical development
The development of the prolonged-release tablet is satisfactory performed and explained. The excipients used are common in the manufacture of prolonged-release tablets. Hypromellose is used to control the drug release from the tablet matrix. The packaging is usual and suitable for the product at issue. The MAH has provided a justification for not performing a bioequivalence study; a Level A IVIVC has been established, and the IVIVC is used as a surrogate for bioequivalence studies.
The core tablet of the 150 mg strength has the same qualitative composition as the other existing strengths. The film coat is qualitatively the same as that used for the 400 mg strength. All strengths are quantitatively different. The excipients are usual for this dosage form in these concentrations and described in several pharmacopoeia. Additional in-house specifications are set for hypromellose 2208.

The specifications for hydroxypropoxy (HP) content and viscosity are adequate to control the quality of the excipient.

Manufacturing process
The drug product is manufactured using a wet granulation, compression and film coating process. Adequate in-process controls are included. As the production process is a non-standard process, assessment was also performed by the Netherlands Health Care Inspectorate in the formal application. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 batches manufactured at each site in accordance with the relevant European guidelines.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications include tests for appearance, identification, assay, degradation products, dissolution, dose uniformity and microbial quality. Batch analysis data have been provided for three production scaled batches from each manufacturing site. All batches comply with the proposed specification. The specification limits are based on the registered Seroquel XR tablets and are acceptable.

Stability tests on the finished product
Stability data has been obtained during storage at 25 ºC/60% RH, 30 ºC/65% RH, 40 ºC/75% RH and 50 ºC/ambient humidity. There were no significant changes for any tests at any condition, including no increase in N-oxide after 12 months. The stability results show that the drug product is stable at long-term, intermediate and accelerated storage conditions, as well as under light, heat and moisture stress. On the basis of the currently available data, a shelf life of 24 months could be granted. However, the proposed shelf life of 36 months for the 150 mg strength is supported by the approved shelf life of 36 months for the other strengths. Therefore, a shelf life of 36 months was granted. Bracketing can be applied especially since the qualitative composition is comparable with the 400 mg strength. The results of the ongoing studies with the 150 mg product strength will be submitted when available.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient of animal origin and is derived from milk fit for human consumption. Scientific data and/or certificates of suitability issued by EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal product has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a line extension of Seroquel XR 50, 200, 300 and 400 mg tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
In line with current legislation, an environmental risk assessment has been undertaken for quetiapine. The use of quetiapine fumarate is likely to result mainly in metabolites and, to a lesser extent, the active moiety entering the environment, since it is almost completely metabolised after intake. Based on the physicochemical and fate properties of quetiapine fumarate, it is predicted that most of the active moiety (quetiapine) will be partitioned into the aqueous phase during wastewater treatment. The aqueous streams containing quetiapine will then, subsequently, be passed to the aquatic environment. In the aquatic environment, quetiapine is not likely to be hydrolytically degraded, and there is no evidence to suggest that biodegradation will be significant. However, as the octanol/water partition coefficient, log Dow is < 3, quetiapine is not likely to bioaccumulate in aquatic organisms.
The PEC/PNEC (Predicted Environmental Concentration/Predicted No Effect Concentration) ratios for microorganisms, surface water and ground water are all below 0.1, and the risk of bioaccumulation is low. In addition, the fate analysis shows no reason for concern for the terrestrial compartment. In conclusion, the fate and effects analysis has not identified a potential risk to the environment as a consequence of the

use of quetiapine. Since this application is a line extension of an already existing product for which an increase of the emission of quetiapine into the environment is not expected, no further action is needed.
The product does not contain any other component which results in an additional hazard to the environment during storage, distribution, use and disposal.

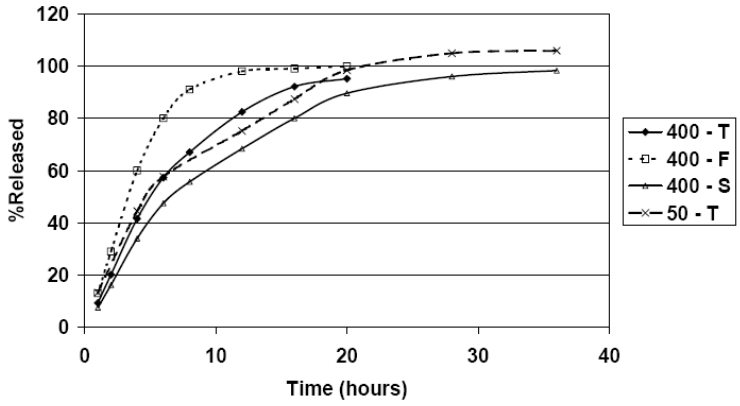
II.3 Clinical aspects

Pharmacokinetics

Quetiapine fumarate is a well-known active substance with established efficacy and tolerability.
For this line extension, the MAH has submitted dissolution data and an IVIV-C (in-vitro-in-vivo correlation) model, demonstrating that the results provided for the Seroquel XR 50, 200, 300 and 400 mg tablets can be extrapolated to the 150 mg prolonged release tablets. This IVIV-C model has been submitted during the first application back in 2007 for the 50/200/300/400 mg XR formulation (NL/H/0156/08-011/MR).

IVIV-C model
In short, two 400 mg formulations with a faster and slower in-vitro dissolution rate were specifically developed for this study to test the model (see figure F1 below for differences in dissolution profiles). The MAH also performed an in-vivo study (001) to validate the model. In this study the PK profile of the regular tablets, and the tablets with fast and slow dissolution rate were established. Based on the in-vitro data, the level A IVIV-C model predicted the in-vivo absorption profile well (C_{max} and t_{max} within 10% deviation Predicted-Observed data) for both the product to be marketed and the test-products with slower and faster dissolution. The IVIVC was externally validated with Seroquel XR 50 mg, which is qualitatively the most different from the 400 mg strength product with respect to the amount of active to excipient ratio. The IVIV-C model predicted the plasma levels after a 50 mg dose satisfactorily.

Figure F1 **In vitro dissolution of SEROQUEL XR used to establish IVIVC**



T = product to be marketed, F = fast formulation, S = slow formulation

In principle, the IVIVC model is applicable to Seroquel XR 150 mg tablets, which have the same qualitative composition as the other Seroquel XR tablets and a similar release mechanism as Seroquel XR 50, 200, 300 and 400 mg tablets. Like the other tablet strengths, the 150 mg tablets consist for 30% of hypromellose 2208, the key excipient which controls the extended release of quetiapine over a period of 1 day. Moreover, kinetics of quetiapine were linear between a dose range of 50-400 mg Seroquel XR tablets. Furthermore, the IVIVC model is applicable to the Seroquel XR 150 mg tablets based upon a similar dissolution profile across all strengths of Seroquel XR tablets. Comparison of dissolution profiles from different manufacturing sites revealed that the IVIVC model is site independent, as the dissolution profiles from these sites are similar.

The member states agreed that no further clinical PK studies are necessary for the line extension of the 150 mg tablet to the already approved range of the 50-200-300-400 mg XR tablets. No unexpected release from the 150 mg tablets is expected, based on the similarity if the dissolution profile of the 150 mg tablets compared to the other strengths, and the linear relationship between the in-vitro dissolution profile and absorption in-vivo.

Clinical Safety

Clinical trial exposure
A total of 14,992 subjects have been exposed to quetiapine IR or XR in 94 clinical trials until 15 October 2007 of which 7746 in blinded randomised trials. Most studies involved acute therapy (<26 weeks) and some longer-term studies (exposure >26 weeks) have been conducted.
Most clinical trials excluded patients with known serious illness (e.g. heart failure, renal or hepatic failure) or history of poor psychiatric outcomes such as recent suicide attempts. Also limited information is available on elderly population, paediatric population, pregnant or lactating women and patients of different or select ethnic or racial origin. The above populations will be included in the Risk Management Plan (RMP) and appropriate pharmacovigilance/risk minimization measures will be identified for each of them.

Post-marketing exposure
Post-marketing exposure through 31 July 2007 has been estimated to be 25.9 million patients worldwide, 15.9 million in the US and 10 million patients outside the US.
For the XR formulation a total of 20 cases have been reported up to 17 December 2007. Somnolence, sedation, dizziness and nightmares were most frequently reported; no new trends were identified.
Up to 12 November 2007 a total of 93 reports of use of quetiapine in the indication bipolar depression have been reported, of which 24 were serious and 69 non-serious. There were no fatal cases. Somnolence, weight increase, dry mouth and dizziness were most frequently reported. No new trends were identified.

Risk management plan
The submitted Risk management plan, dated 15 January 2008, was already submitted as part of the pending type II variations NL/H/0156/08-011/II/048+049. It supersedes the previous version of the RMP (dated 18 September 2006 regarding the XR formulation of quetiapine for the treatment of schizophrenia) and has been updated with new data from clinical studies with the IR formulation of quetiapine in bipolar depression, the XR formulation in bipolar depression and bipolar mania and the IR formulation in a long-term study in schizophrenia.
In addition, long-term data is sparse for the XR formulation of quetiapine in all indications (bipolar depression, bipolar mania and schizophrenia) and for the IR formulation in the use of bipolar depression. Long-term use will be included as limited information in the RMP with appropriate pharmacovigilance and risk minimisation measures to be taken.
Following comments from the MEB, the MAH committed to update the RMP. These updates will be delivered in the new version of the RMP that will be submitted for assessment in October 2008 with the planned new indication application for the treatment of Generalised Anxiety Disorder (GAD).

Pharmacovigilance system
The RMS considers that the Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Product information

Readability test
The MAH has submitted combined product information for the already approved strengths and Seroquel XR 150 mg. Recently a type II variation to update the product information, NL/H/0156/08-011/II/048 has been approved. The changes are incorporated in the product information for Seroquel XR 150 mg as well.

The Seroquel XR Patient Information Leaflet (50, 200, 300, 400 mg) has been the subject of a focussed Readability test, to build on the bridging strategy to the IR Patient Information Leaflet. This approach was approved in the MRP NL/H/0156/08-011/MR for Seroquel XR. As limited new information was included in the PIL for the 150 mg XR application, a bridging strategy was applied to the User Testing of the Patient Information Leaflet.
The MAH committed to perform a User Test on the XR PIL in the first half of 2009, to address the considerable new information that has been included through type II variations 48, 49, 50, 57 and 59.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Seroquel XR 150 mg, prolonged release tablets has a proven chemical-pharmaceutical quality and is a legitimate line extension of Seroquel XR 50, 200, 300 and 400 mg, prolonged release tablets, which have been registered via MRP procedure NL/H/0156/08-011/MR.

The MAH has provided dissolution data and an IVIV-C model, demonstrating that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the authorised Seroquel XR tablets

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the other Seroquel XR products. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile was demonstrated for Seroquel XR 150 mg, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 19 November 2008. Seroquel XR 150 mg, prolonged release tablets was authorised in the Netherlands on 17 December 2008.

A European harmonised birth date has been allocated (31 July 1997) and subsequently the first data lock point for quetiapine is July 2009. The first PSUR will cover the period from November 2008 to July 2009, after which the PSUR submission cycle is 1 year.

The date for the first renewal will be: 31 March 2012.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to submit the results of the ongoing stability studies with the 150 mg tablets up to the granted shelf-life.

Readability test

- The MAH committed to perform a user test on the XR PIL in the first half of 2009, in order to address the considerable new information.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
IVIV-C	In-Vitro-In-Vivo Correlation
IR	Immediate Release
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PEC	Predicted Environmental Concentration
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PNEC	Predicted No Effect Concentration
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the indication- Bipolar Disorder including: - preventing recurrence in bipolar disorder (manic, mixed or depressive episodes)	NL/H/0156/ 012/II/057	II	27-12-2008	18-9-2009	Approval	Y, Annex I
Update of the SPC with respect to suicidality, CFK, thrombocytopenia and abnormal dreams and nightmares.	NL/H/0156/ 012/II/059	II	18-8-2008	20-2-2009	Approval	N
Update SPC sections 4.2, 4.4, 4.8, 5.1 and 5.2 to reflect available data from clinical trials in paediatric patients.	NL/H/0156/ 012/II/061	II	21-12-2009	12-1-2010	Approval	N
To update the safety information for quetiapine fumarate in relation to weight gain, prolactin, irritability, increased appetite, galactorrhea, and falls consequently revising the Package insert. An update to the Detailed Description of the Pharmacovigilence System.	NL/H/0156/ 012/II/062	II	8-1-2009	2-7-2009	Approval	N
Change in the manufacturer of the active substance or starting material/reagent/intermediate in the manufacturing process where no Ph.Eur Certificate of Suitability is available; New manufacturer (replacement or addition)	NL/H/0156/ 012/IB/063	IB	17-2-2009	19-3-2009	Approval	N
Revision to SmPC Pneumonia (section 4.4), HDL (sections 4.4 and 4.8), QT (sections 4.4, 4.5 and 4.9) and TD (sections 4.4 and 4.8).	NL/H/0156/ 012/II/066	II	1-8-2009	30-10-2009	Approval	N
Change to batch release arrangements and quality control testing of the finished product; Replacement or addition of a manufacturer responsible for batch release - not including batch control/testing	NL/H/0156/ 012/IA/067	IA	21-10-2009	4-11-2009	Approval	N
Change in the manufacturer of the active substance or starting material/reagent/intermediate in the manufacturing process of the active substance where no Ph. Eur. Certificate of Suitability is available; New manufacturer (replacement or addition)	NL/H/0156/ 012/IB/068	IB	21-10-2009	23-11-2009	Approval	N
Minor change in the manufacturing process of the active substance	NL/H/0156/ 012/IB/069	IB	21-10-2009	23-11-2009	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; Secondary packaging site for all types of pharmaceutical forms, Primary packaging site - Solid pharmaceutical forms, e.g. tablets and capsules	NL/H/0156/ 012/IA/071	IA	21-10-2009	4-11-2009	Approval	N
Update of SPC section 4.8 in relation to dysarthria frequency.	NL/H/0156/ 012/II/072	II	13-11-2009	12-1-2010	Approval	N
Updated to the detailed description of the pharmacovigilance system	NL/H/0156/ 012/II/073	II	13-11-2009	12-1-2010	Approval	N

Change in the name and/or address of a manufacturer of the finished product	NL/H/0156/ 012/IA/075	IA	4-1-2010	18-1-2010	Approval	N

ANNEX I – Addition of the indication *Recurrence prevention in bipolar disorder* (NL/H/0156/012/II/57)

On 27 December 2008 a type II variation was started for addition of the indication *Recurrence prevention in bipolar disorder.* The overall benefit-risk profile was positive, and therefore the variation was approved by the member states on 18 September 2009.

Bipolar disorders are psychiatric disorders in which a disturbance in mood is the predominant feature. Bipolar I disorder is characterized by one or more manic or mixed episodes, usually alternating with major depressive episodes. Bipolar II disorder is characterized by one or more major depressive episodes and at least one hypo-manic episode.
At the moment, lithium is the only other compound registered for this indication.

Following CHMP guidelines for the indication recurrence prevention (CPMP/EWP/567/98) efficacy has to be demonstrated in long term (at least one year) prophylactic treatment studies with the purpose of preventing recurrence of (hypo-)manic and depressive symptoms (new episodes). A possible design is a withdrawal trial versus placebo and active comparator (three-arm). Recurrence is defined as re-emergence of symptoms (new episode) after a time with no or minimal symptoms using the same scales as in the acute studies (e.g. YMRS, MDRS). Patients with bipolar I disorder that are in full remission should be included in the study. To demonstrate recurrence prevention, it is recommended to include patients with a reasonably high recurrence rate only. However, patients included in the study should be free of manic/depressive symptoms for a sustained period of time at the start of the study, so that if manic or depressive symptoms occur, recurrence can be distinguished from relapse.

Clinical efficacy
No efficacy studies with Seroquel XR have been performed. Reference is made to the studies performed with the IR formulation.
The Seroquel XR formulation may be considered effective in the proposed indication in view of:

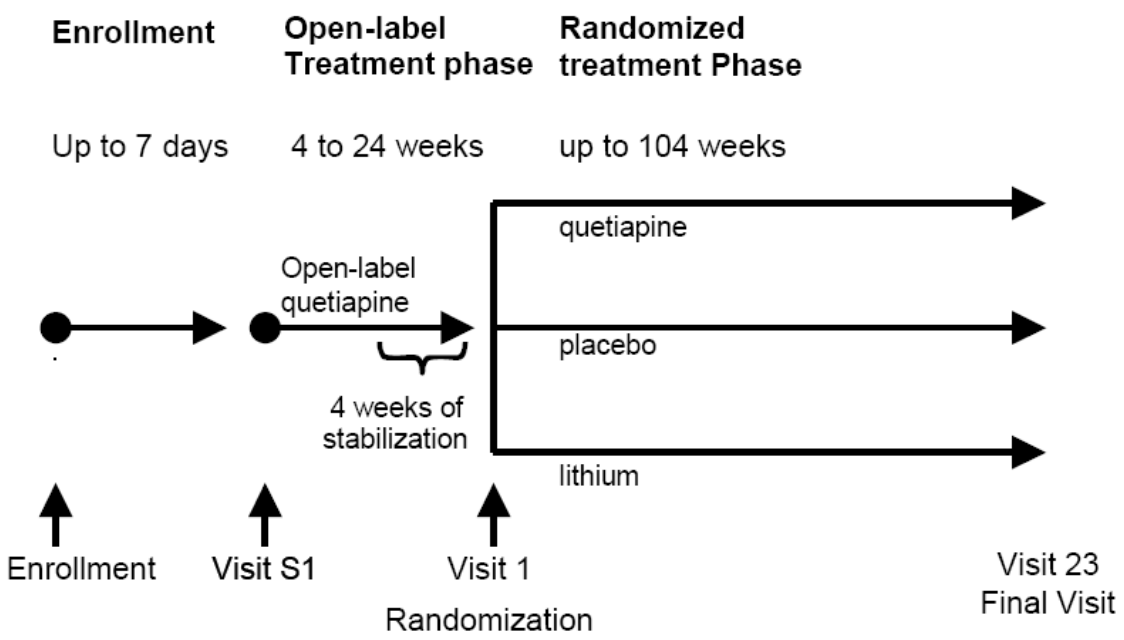
- the approved indication *recurrence prevention in bipolar depression* for Seroquel IR.
- the similarities in overall exposure for equivalent doses of the quetiapine XR and IR formulations.
- similar safety profiles of the XR and IR formulations.
- the positive evaluation of the previously submitted data on quetiapine XR in the treatment of mania, treatment of depressive episodes in the framework of bipolar disorder.

Quetiapine XR vs. IR
The quetiapine XR formulation is thought to provide advantages over the IR formulation by permitting once-daily dosing with the potential for an increased adherence. In addition, the quetiapine XR formulation exhibits a longer tmax but a similar AUC in comparison with the same daily dose of the IR formulation. These properties should allow faster titration to steady state because of fewer or less-severe side effects at start of dosing associated with a more rapid rise to Cmax.

Clinical study
Design
The clinical documentation submitted to support the new indication for the IR formulation comprises one Phase 3 study. This was a multi-centre, randomized, parallel-group, double-blind, placebo-controlled phase III study. The design of the study was a withdrawal design, starting with open-label treatment lasting between 4 and 24 weeks, followed by a randomised withdrawal phase up to 104 weeks. During this withdrawal phase the efficacy and safety in preventing recurrence in adults bipolar I patients was tested against placebo and an active comparator (lithium).
The purpose of the open–label treatment phase was to achieve clinical stabilization for at least 4 weeks. In the open-label treatment phase, patients began or continued on an oral dose of open-label quetiapine, 300 mg to 800 mg daily in divided doses, with a recommended target dose of 600 mg/day.
Treatment with open-label quetiapine continued until patients met all the inclusion criteria and none of the exclusion criteria for randomization (see below). Patients who did not meet the eligibility criteria for randomization at week 24 were withdrawn from the study. Other antipsychotic and psychoactive

medications (e.g. antidepressants, mood stabilizers and anxiolytics) could be used during open-label phase, with exception of the last 4 weeks prior to randomization. The use of other psychoactive drugs was restricted during the same time period (e.g. < 2 mg of lorazepam).
At the start of the randomisation, open-label quetiapine tablets were replaced with blinded tablets of quetiapine, placebo or lithium. The dose of blinded quetiapine (or placebo) could be adjusted as clinically indicated within the dose range of 300 mg to 800 mg/day and the dose of blinded lithium (or placebo) could be adjusted within the dose range of 600 mg to 1800 mg/day all through the randomized treatment phase. Dose adjustments for lithium were made to achieve target trough serum concentrations of 0.6 mEq/L to 1.2 mEq/L. All patients had blood tests in order to keep the blind.

Figure S 1 Study flow chart



Population studied
Inclusion criteria:

- Males and females > 18 years of age
- Diagnosis of Bipolar I Disorder as defined by DSM IV
- An acute manic, mixed or depressed episode at enrolment, with or without psychotic features;
- Experienced a past manic, depressed or mixed episode within 26 weeks, as documented by medical records. If the patient had the index episode within 26 weeks prior to enrolment, the episode should have been treated with quetiapine, which must not have been interrupted for more than 2 weeks continuously since the start of treatment.
- Patients should have had at least 1 manic, depressed or mixed episode in the 2-year period prior to the index episode.
- Female patients of childbearing potential must be using a reliable method of contraception.

There was no severity minimum criterion for entry.

Exclusion criteria:

- Diagnosis of an anxiety disorder as defined by DSM-IV, which was treated with medication within the past year;
- Substance or alcohol dependence at enrolment (except dependence in full remission, and except for caffeine or nicotine dependence), as defined by DSM-IV criteria;

- Opiate, amphetamine, barbiturate, cocaine, cannabis, or hallucinogen abuse by DSM-IV criteria within 4 weeks prior to enrolment;
- Unstable or inadequately treated medical illness (e.g. angina pectoris, hypertension and DM) as judged by the investigator.

Primary endpoint
To evaluate the efficacy of quetiapine versus placebo in increasing time from randomization to recurrence of a mood event in patients with Bipolar I Disorder. The primary endpoint was analysed as time to event of a mood episode (being depression, mania or mixed episode, whichever came first). The recurrence of a mood episode was defined as fulfilling at least 1 of the following:
- Initiation of an antipsychotic, antidepressant, mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a manic, depressed or mixed event;
- hospitalization for a manic, depressed or mixed event;
- Young Mania Rating Scale (YMRS) score ≥20 at 2 consecutive assessments or at the final assessment if the patient discontinues, or Montgomery-Asberg Depression Rating Scale (MADRS) score ≥20 at 2 consecutive assessments or at the final assessment if the patient discontinues;
- Discontinuation from the study by the patient if, in the opinion of the investigator, the discontinuation was due to a manic, depressed or mixed event.

Secondary endpoints
To evaluate the efficacy of quetiapine versus placebo in increasing time from randomization to recurrence of a manic event in patients with Bipolar I Disorder. The secondary endpoint was analysed as time to event of a manic event, whereas manic event was defined as fulfilling at least 1 of the following:
- Initiation of an antipsychotic, mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a manic event or a mixed event with predominantly manic symptoms;
- hospitalization for a manic event or a mixed event with predominantly manic symptoms;
- YMRS score ≥20 for 2 consecutive assessments, or YMRS score ≥20 at final assessment if the patient discontinues;
- discontinuation from the study by the patient if, in the opinion of the investigator, the discontinuation was due to a manic event or a mixed event with predominantly manic symptoms.

To evaluate the efficacy of quetiapine versus placebo in increasing time from randomization to recurrence of a depressive event in patients with Bipolar I Disorder. The secondary endpoint was analysed as time to event of a manic event, whereas depressive event was defined as fulfilling at least 1 of the following:
- initiation of an antidepressant, mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a depressed event or a mixed event with predominantly depressed symptoms;
- hospitalization for a depressed event or a mixed event with predominantly depressed symptoms;
- MADRS score ≥20 for 2 consecutive assessments, or MADRS score ≥20 at final assessment if the patient discontinues;
- discontinuation from the study by the patient if, in the opinion of the investigator, the discontinuation was due to a depressed event or a mixed event with predominantly depressed symptoms.

Study results
In the open-label phase, all patients received a flexible dose of 300 to 800 mg/day of quetiapine, the median daily dose in the open label phase was 497 mg. After the open label treatment phase (up to 24 weeks to stabilize) approximately 55% of the patients entered the randomization phase. A total of 6.8% of the patients discontinued due to AEs and 12.1% were not willing to continue.

The number of patients included in the randomised phase was 1172 patients (ITT population) The mean YMRS and MADRS scores at randomisation are depicted in the table below.

	Quetiapine (N =404)	Placebo (N =404)	Lithium (N=364)	Total (N=1172)

YMRS at randomization				
N[a]	403	404	364	1171
Mean (SD)	3.88 (3.658)	3.69 (3.549)	3.74 (3.475)	3.77 (3.563)
Median	3.00	3.00	3.00	3.00
Min to max	0 to 14	0 to 13	0 to 12	0 to 14
MADRS at randomization				
N[a]	404	403	364	1171
Mean (SD)	3.55 (3.482)	3.41 (3.412)	3.34 (3.467)	3.44 (3.452)
Median	3.00	2.00	2.00	2.00
Min to max	0 to 12	0 to 14	0 to 19	0 to 19

a = missing observation

The number of premature discontinuation during the randomised treatment phase other than recurrence of a mood event was low (± 20%). This is supporting the internal validity of the study by restricting the introduction of biases (e.g. if considerable number of patients discontinue due to for instance AEs this could lead to selection bias). In addition, a low number of patients discontinued due to AEs (3.8% compared to 6.8% during open-label), suggesting possible fewer safety problems with extended quatiapine exposure (habituation). The table below presents discontinuation and reason during the randomised phase.

Table E- 5 Premature discontinuation from randomized treatment phase (ITT population)

	Quetiapine N=404 n (%)	Placebo N=404 n (%)	Lithium N=364 n (%)	Total N=1172 n (%)
All patients randomized and included in ITT	404 (100.0)	404 (100.0)	364 (100.0)	1172 (100.0)
Premature discontinuation due to a mood event	87 (21.5)	202 (50.0)	89 (24.5)	378 (32.3)
Premature discontinuation due to other reason than mood event	68 (16.8)	80 (19.8)	99 (27.2)	247 (21.1)
Eligibility criteria not fulfilled	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Adverse event	14 (3.5)	10 (2.5)	20 (5.5)	44 (3.8)
Lack of therapeutic response	1 (0.2)	2 (0.5)	1 (0.3)	4 (0.3)
Subject not willing to continue study	32 (7.9)	40 (9.9)	36 (9.9)	108 (9.2)
Subject lost to follow up	6 (1.5)	12 (3.0)	21 (5.8)	39 (3.3)
Incorrect randomization	1 (0.2)	4 (1.0)	3 (0.8)	8 (0.7)
Severe non-compliance to the CSP as judged by Investigator or AstraZeneca	6 (1.5)	9 (2.2)	10 (2.7)	25 (2.1)
Other	8 (2.0)	3 (0.7)	7 (1.9)	18 (1.5)
Completed randomized treatment phase[a]	249 (61.6)	122 (30.2)	176 (48.4)	547 (46.7)

[a] Treated for up to 104 weeks or not discontinued until study termination.
ITT Intent-to-treat. N Number of patients in treatment group. n Number of patients.
Note: Patients discontinued due to a mood event had "Development of study specific criteria" marked in the CRF module for study termination.
Note: Percentages are calculated as n/N.
Table derived from Table 11.1- 3 of the Study 144 CSR in Module 5

Results – primary efficacy outcome

Table 1 presents the number of recurrences in placebo, quetiapine and lithium groups during the interim analysis ITT and ITT population.

Table 1 Patients fulfilling a mood event criteria (center 1005 excluded)

	ITT Population			Interim-ITT Population	
	Quetiapine N = 386 N (%)	Placebo N = 386 N (%)	Lithium N = 349 N (%)	Quetiapine N = 350 N (%)	Placebo N = 348 N (%)
Number of patients with mood event	88 (22.8)	202 (52.3)	90 (25.8)	58 (16.6)	152 (43.7)
Initiation of medication	66 (75.0)	154 (76.2)	67 (74.4)	NA	NA
Hospitalization	37 (42.0)	67 (33.2)	20 (22.2)	NA	NA
YMRS>=20 or MADRS>=20	78 (88.6)	178 (88.1)	80 (88.9)	NA	NA
Discontinuation	14 (15.9)	30 (14.9)	15 (16.7)	NA	NA

Note: Patients in the ITT population can fulfill more than one criteria. Percentages on the total row are calculated as n/N*100, other percentages are calculated as n divided by Number of patients with a mood event *100

MADRS Montgomery-Asberg Depression Rating Scale. YMRS Young mania rating scale. N Number of patients in treatment group. n number of patients.

Table 3 presents the statistical tests and 95% confidence intervals for the differences (placebo vs. quetiapine in the interim-ITT = primary analysis)

Table 3 Analysis of time to recurrence of a mood event (Interim-ITT population, center 1005 excluded)

	Quetiapine vs Placebo $N_{Quetiapine}=350/N_{Placebo}=348$
Hazard Ratio	0.26
95% CI	0.19,0.35
p-value	<.0001

CI Confidence interval. ITT Intent-to-treat. N Number of patients in treatment group.

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The MAH found that center 1005 tended to use insufficient documentation practices, and that certain deficiencies in monitoring at this center may have been at hand as evidenced by the questionable suitability of some patients. Therefore, center 1005 was excluded from analysis.
In the primary analysis, quetiapine significantly increased the time to recurrence of a mood event, compared with placebo in the interim ITT population.

Table 39 Analysis of time to recurrence of a mood event by index episode, per MADRS or YMRS criteria only (ITT population)

	Quetiapine N=404		Placebo N=404		Lithium N=364		Quetiapine vs. Placebo		Lithium vs. Placebo		Quetiapine vs. Lithium	
	N[a]	n[b]	N[a]	n[b]	N[a]	n[b]	HR	95% CI	HR	95% CI	HR	95% CI
Index episode[c]												
Manic	212	44	223	91	193	46	0.32	0.22, 0.46	0.50	0.35, 0.71	0.68	0.45, 1.03
Mixed	78	13	66	31	72	15	0.30	0.15, 0.58	0.50	0.27, 0.94	0.61	0.29, 1.31
Depressed	114	22	115	58	99	24	0.26	0.16, 0.44	0.45	0.28, 0.73	0.61	0.34, 1.10

[a] Number of patients in subgroups.
[b] Number of patients with events in subgroups.
[c] DSM-IV diagnosis of bipolar I disorder, most recent episode.
ITT Intent-to-treat. N Number of patients in treatment group. CI Confidence interval. HR Hazard ratio.
Table corresponds to Table 11.2.1- 16

Lithium also significantly increased the time to recurrence of a mood event (p<0.0001), compared to placebo, thereby confirming the assay sensitivity of the study.

The significantly increased time to recurrence of a mood event was irrespective of index episode in the ITT population (table below, with the total number of recurrences).

Index	Quetiapine Ntotal = 404 **At risk**	Quetiapine **Events**		Placebo Ntotal = 404 **At risk**	Placebo Events		HR (quetiapine vs. placebo)
Manic	212	50	24%	223	108	48%	0.31 (.22-.44)
Depression	78	14	18%	66	37	56%	0.26 (.14-.48)
Mixed	114	27	24%	115	63	54%	0.29 (.18-.46)

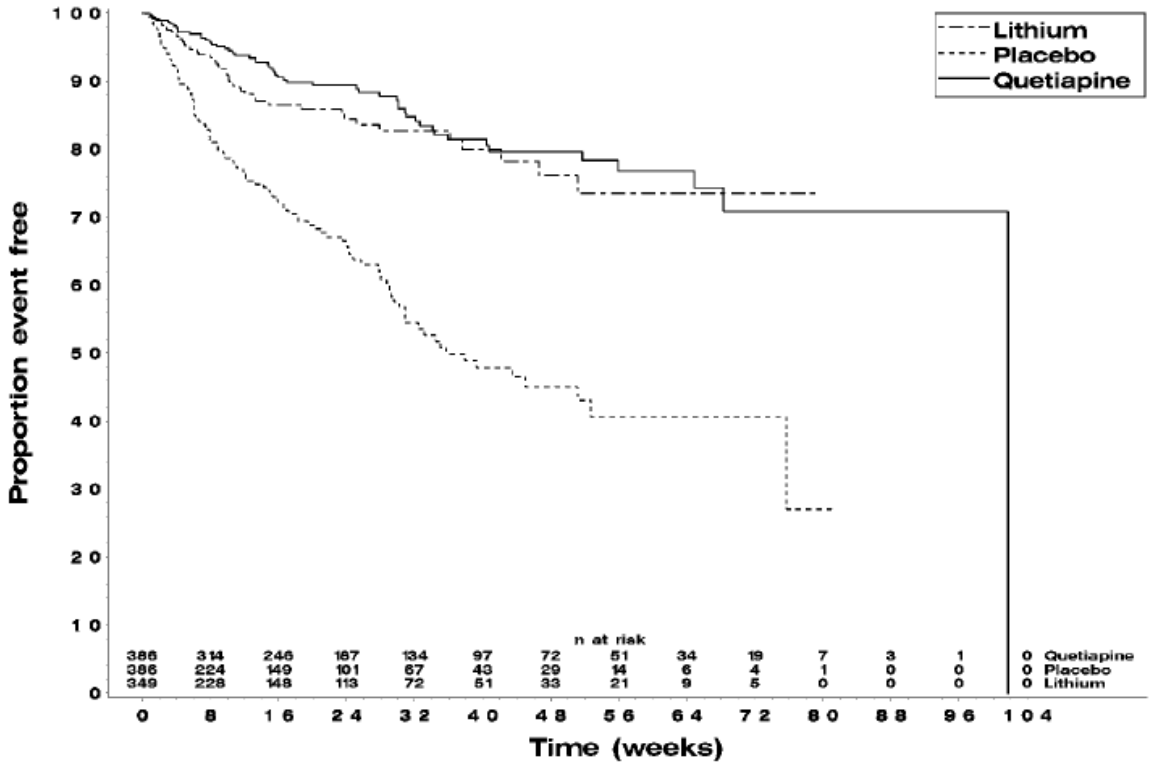
The demonstrated efficacy of quetiapine in the ITT population was not restricted to any specific subgroup (age, sex, race, episode, cycling frequency, or region). In addition, the superiority of quetiapine vs. placebo demonstrated for the ITT population was supported by the results in the PP population.

Secondary efficacy outcome
Following CHMP guideline, for a claim prevention of recurrence in bipolar disorder this must be demonstrated for other poles of the mood spectrum (manic and depression). This is demonstrated in the secondary analysis presented below.

Mania
A total of 53 patients (13.7%) experienced a manic event during the randomization phase in the quatiapine group, 44 patients (12.6%) in the lithium group and 121 patients (31.3%) in the placebo group (table below, also overall and depressed events).

	Mood disorder N	%	Manic event N	%	Depressed event N	%
Quetiapine	88	22.8	53	13.7	35	9.1
Lithium	90	25.8	44	12.6	46	13.2
Placebo	202	52.3	121	31.3	81	21

The figure below is demonstrating the difference in time to recurrence of a manic event in Kaplan Meier curves between treatment groups.

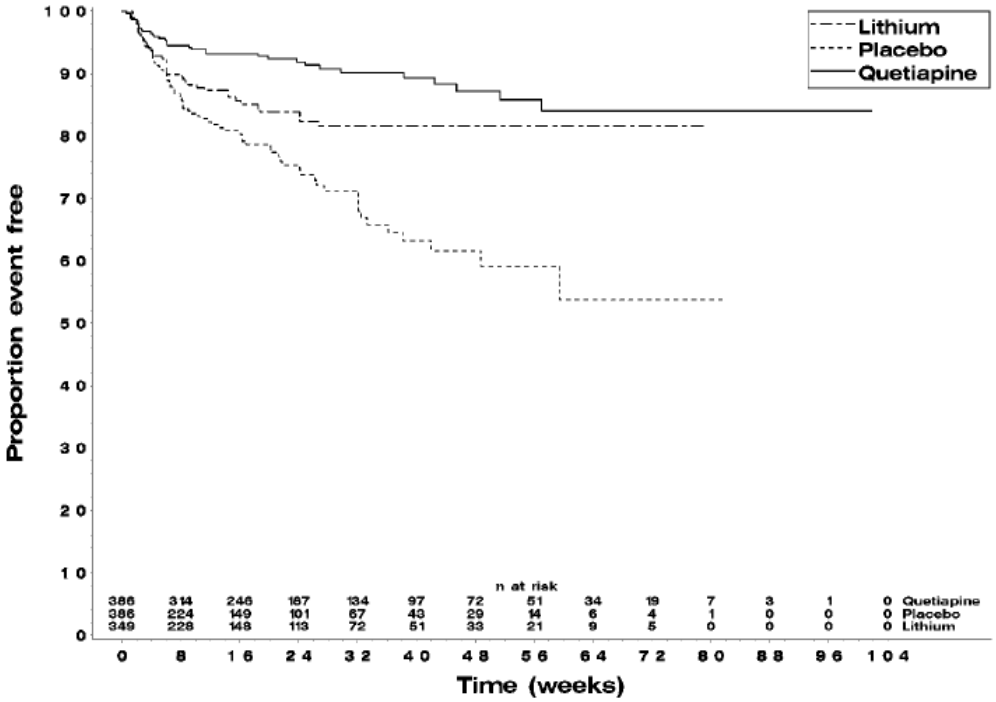


In conclusion, quetiapine significantly increased the time to recurrence of a manic event, compared with placebo in the ITT population (hazard ratio 0.28, 95% CI .2-.39, risk reduction 72%, p<0.0001).

Depression

A total of 35 patients (9.1%) experienced a depressed event during the randomization phase in the quatiapine group, 46 patients (13.2%) in the lithium group and 81 patients (21%) in the placebo group (table above).

The figure below is demonstrating the difference in time to recurrence of a depressive event in Kaplan Meier curves between treatment groups.



In conclusion, quetiapine significantly increased the time to recurrence of a depressive event, compared with placebo in the ITT population (hazard ratio 0.30, 95%CI .2-.45, risk reduction 70%, p<0.0001)

Dose recommendations

The entire quetiapine dose range of 300 to 800 mg/day was used at the time of randomization in this study. The mean of open-label median daily dose was 497 mg and the median dose was 546 mg during randomization phase. Quetiapine was superior to placebo in increasing time to a mood event, irrespective of the dose patients were receiving at randomization: the HR ranged from 0.26 to 0.33 and the lowest HR was observed in the highest dose category, > 600 to ≤ 800 mg quetiapine.

A percentage of 89% ((141+138+81)/404) of quetiapine patients had the same median dose during randomized treatment as the dose they had at randomization, after stabilization following acute treatment. These data suggest that most patients stayed on the same dose during randomized treatment phase as the dose they had at randomization.

Clinical safety

The clinical program for the development of quetiapine in bipolar disorder recurrence prevention treatment includes 3 double-blind placebo-controlled studies; 2 studies investigating the efficacy of quetiapine vs placebo when used as adjunct to lithium or valproate in increasing time to recurrence of a mood event in patients with bipolar I disorder, and 1 study using quetiapine as monotherapy for recurrence prevention in bipolar I disorder. These studies had an open-label stabilisation phase followed by a randomised withdrawal design.

In the monotherapy study (including the open-label phase which comprised of 4-24 weeks) 115 patients have been exposed to quetiapine (monotherapy) for at least 12 months, 66 for at least 15 months, 35 for at least 18 months, 16 for at least 21 months and 2 for at least two years. The study contained a limited number of elderly patients (45) of which only 9 have been treated with quetiapine in the randomised phase of the study.

One new important identified risk and one new important potential risk have been identified, which are withdrawal symptoms and rhabdomyolysis respectively. These two risks had been identified, but do not relate specifically to the newly applied indication.

Conclusion

The studies performed with Seroquel IR formulation indicate that quetiapine is effective in bipolar disorder recurrence prevention treatment. Bridging to these results for Seroquel XR is acceptable. The MAH has

provided sufficient answers to the questions posed by the member states. The indication *recurrence prevention in bipolar depression* was therefore approved.