CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Quetiapine XR AstraZeneca 50 mg, 150 mg, 200 mg, 300 mg and 400 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/1983/001-005/DC
Registration number in the Netherlands: RVG 106971, 106978-106981

28 February 2011

Pharmacotherapeutic group:	antipsychotics; diazepines, oxazepines and thiazepines
ATC code:	N05AH04
Route of administration:	oral
Therapeutic indication:	schizophrenia; moderate to severe manic episodes; major depressive episodes (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	3 November 2010
Concerned Member States:	Decentralised procedure with FR
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 Quetiapine XR AstraZeneca 50 mg, 150 mg, 200 mg, 300 mg and 400 mg, prolonged-release tablets from AstraZeneca B.V. The date of authorisation was on 3 November 2010 in the Netherlands.

The product is indicated for

- 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 in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment.
- add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy. Prior to initiating treatment, clinicians should consider the safety profile of Quetiapine XR AstraZeneca (see Section 4.4 of the approved SPC).

A comprehensive description of the indications and posology is given in the SPC.

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 a full application for an additional marketing authorisation in the Netherlands (Quetiapine XR AstraZeneca) and a new marketing authorisation in France (Xeroquel LP). The innovator product Seroquel XR has been registered in the Netherlands since 21 August 2007 by AstraZeneca as a line extension to the existing Seroquel immediate-release tablets. A number of EU countries recognised the marketing authorisation through procedure NL/H/0156/08-011/MR. As France was not among these CMS, the MAH seeks to register the product in FR through this DCP.

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

The submitted quality, non-clinical and clinical parts of the dossier are identical to the dossier for Seroquel XR (NL/H/0156/008-012) and are therefore considered approvable by the RMS. The application for Seroquel XR was a line extension of the dossier presented for procedure NL/H/0156/001-007/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 submitted dissolution data and an IVIV-C (in-vitro-in-vivo correlation) model. For assessment and a discussion of these data, refer to the EPARs for NL/H/0156/008-011/MR and NL/H/0156/012/DC, concerning Seroquel XR.

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
Quetiapine XR AstraZeneca 50, 150, 200, 300 and 400 mg prolonged release tablets contain as active ingredient quetiapine fumarate corresponding to 50, 150, 200, 300 and 400 mg of quetiapine, respectively. The different tablet strengths are qualitatively but not quantitatively identical. They can be easily distinguished by their colour and inscription.

Quetiapine XR AstraZeneca 50 mg tablets are peach-coloured and engraved with "XR 50" on one side.
Quetiapine XR AstraZeneca 150 mg tablets are white and engraved with "XR 150" on one side.
Quetiapine XR AstraZeneca 200 mg tablets are yellow and engraved with "XR 200" on one side.
Quetiapine XR AstraZeneca 300 mg tablets are pale yellow and engraved with "XR 300" on one side.
Quetiapine XR AstraZeneca 400 mg tablets are white and engraved with "XR 400" 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), yellow iron oxide(E172) (50, 200 and 300 mg tablets), red iron oxide (E172) (50 mg tablets).

Pharmaceutical development

In order to reduce the frequency of quetiapine administration and simplifying the treatment initiation schedule, this quetiapine formulation was developed that had to be administered only once daily. All tablet strengths have a unique, but qualitatively related formulation. The formulation studies showed that differences in the proportion of hypromellose had an effect on the dissolution profile of the drug substance. The choice for the composition also involved the *in vivo* plasma profiles generated for different drug product compositions. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The excipients are usual for this dosage form in these concentrations and described in several pharmacopoeia. Additional in-house specifications are set for hypromellose used in the formulation. The packaging is usual and suitable for the products at issue.

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 at least 3 batches per strength 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 at least 3 batches per strength 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. Based on the data provided, a shelf life of 3 years could be granted, with no special storage condition.

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 identical to Seroquel XR 50, 150, 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

The clinical dossier provided is identical to the one for NL/H/0156/008-012, concerning Seroquel XR 50, 200, 300, 400 and 150 mg, respectively. For pharmacokinetic and pharmacodynamic data, reference is made to the Seroquel dossier. A discussion of the clinical studies performed on Seroquel XR is included in the PAR (http://db.cbg-meb.nl/mri/par/nlh-0156-008-009-010-011.pdf). During this procedure several clinical issues have been raised. These are discussed below.

Therapeutic indication
The CMS could not approve of the sub-indication for schizophrenia: *including preventing relapse in stable schizophrenic patients who have been maintained on Seroquel XR* as the indication "treatment of schizophrenia" includes treatment of acute psychotic symptoms, maintenance therapy to control symptoms, and long-term prophylactic treatment (Note for Guidance on the clinical investigation of medicinal products in the treatment of schizophrenia (CPMP/EWP/559/95, 1998)).
In accordance with the comments, this information was removed from the therapeutic indications and only included section 5.1 of the SPC.

Changes in thyroid function
The MAH was requested to submit the cumulative review on 'changes in thyroid function' as post-approval commitment for this procedure to CMS France as well. The cumulative review on 'changes in thyroid function' was submitted in July 2010.

Death
The MAH confirmed that "Sudden death" and "unexplained deaths" will be recorded in the Modified Prescription Event Monitoring (M-PEM) study, one of the 6 studies contained in the Seroquel/Seroquel XR Patient Risk Management Plan. The design of this study enables these outcomes to be captured.

Post-authorisation safety monitoring in new CMS
As SEROQUEL XR will be authorized in France for the first time, the MAH should commit to add specific national measures in France, at least. In the European RMP, the MAH proposed no study within the indication "prevention of recurrence in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment". However, no data regarding the long-term safety of Seroquel XR in patients with bipolar disorder is available. Consequently, the MAH is requested to set up in France post-authorisation safety study investigating this indication in comparison to all other usual treatments. Co-administration with lithium treatment, or previous treatment with lithium is especially of interest.
The MAH stated that one of the main objectives of the PASS programme is to provide longer-term safety data, although exposure will vary across studies and individual patients. Within the programme, the GPRD, PHARMO and M-PEM Studies will all include patients with bipolar disorder, due to their observational design. Analysis of the data from these studies by indication may have limitations but will be conducted and reported where feasible. Co-administration with lithium and other medications treatment will be evaluated in these studies. Due to similarities in diagnosis and treatment of bipolar disorder across Western Europe, the MAH considers these studies relevant to the concern raised by the member states.

In addition, long term safety of Seroquel in patients with bipolar disorder and in combination with lithium (and valproate) has been investigated in the following studies;

- D1447C00126 and D1447C00127 - Evaluate the efficacy of Seroquel versus placebo when used as adjunct with lithium (or valproate) in increasing time to recurrence of a mood event up to 104 weeks of double-blind treatment with Seroquel or placebo.
- D1447C00144 - A lithium treatment group was included in order to assess assay sensitivity (comparison versus placebo) and to provide data for assessing the benefits and risks of continuing Seroquel treatment versus switching to lithium for recurrence prevention in bipolar disorder following 4 to 24 weeks of open-label treatment with
- Seroquel followed by up to 104 weeks of randomised, double-blind treatment with Seroquel, placebo or lithium.

These studies were conducted with the immediate release formulation. However, the safety profile of Seroquel and Seroquel XR has been shown to be consistent in all clinical studies, therefore these are applicable to the assessment of safety of Seroquel XR in the long-term treatment of bipolar disorder.
The MAH stated its belief that the long-term safety in a clinical trial setting has been adequately demonstrated (D1447C00126, D1447C00127 and D1447C00144). This is complemented by an extensive PASS programme being conducted with European patients in the real life setting that will provide long-term safety data in bipolar patients (GPRD, PHARMO and M-PEM). The MAH does not consider an additional study necessary to minimise risk to bipolar disorder patients. However recognising the limited experience of Seroquel XR in France, the MAH agreed to conduct a PASS Study in France in patients with bipolar disorder, subject to post-approval discussions with the member states on the appropriate design and associated feasibility.

Off-label use
As there is a potential for off-label use and misdosing, the MAH is requested to set up a drug utilisation study in France in order to assess the real life use of the product.
The MAH committed to conduct a study of Drug Utilisation in France. In accordance with 'Volume 9A Notice to Applicants' the design of this study will be discussed and agreed with the French Competent Authority prior to commencement.

Educational pieces
In accordance with the conclusions drawn up during variation NL/H/0156/01-012/II/076, the MAH should confirm that the educational piece is submitted to all psychiatrists/GPs and not only handed out when visiting them, as a growing numbers of physicians choose not to receive visitors from pharmaceutical companies. Indeed, the MAH must ensure that Health care professionals who intend to prescribe Seroquel are provided with an SPC and educational information about the risks associated with the use of the product in the different indications. Regarding France, the format of the educational material should be discussed and agreed with the French Competent Authority prior to launch.
The MAH agreed to fulfill this obligation and to distribute educational materials to all relevant physicians in France.

Posology
The member states consider it appropriate to inform prescribers on the lower dose before the higher dose recommended. The following should be included in section 4.2 of the SPC.
For the treatment of depressive episodes in bipolar disorder Seroquel XR should be administered at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group (see section 5.1). Individual patients may benefit from a 600 mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered.
The MAH agrees with this proposal is acceptable and updated the SPC accordingly.

Risk management plan

Version 9 of the Patient Risk Management Plan (PRMP) has been included in the dossier. This version is currently under assessment via type II variation NL/H/156/01-12/11/76 and has not yet been approved. The final assessment is currently pending.
Version 10 will be submitted in September 2010 and will address all comments on Version 9.

Product information

SPC
The MAH agreed to keep the product information from this DCP in line with the product information of the MRP license of Seroquel XR. Consequently the enclosed product information has been updated with all changes approved for the MRP license of Seroquel and Seroquel XR during the DCP procedure. This includes the outcome of the Seroquel article 6(13) referral procedure (EMA/H/A-6(13)/1190) and the worksharing assessment of the quetiapine Periodic Safety Update report (report period 1 Aug 2008 to 31 Jul 2009) (NL/H/PSUR/021/002).
Also, the MAH has agreed to some of the changes suggested by the member states. These changes will be implemented through variations (for this procedure as well as for Seroquel IR and XR) following finalisation of this procedure.

Readability test
The Patient Information Leaflet included in the submission reflects the readability test which has been assessed via type II variation NL/H/156/01-12//II/74. The procedure ended positively on 23 April 2010. As requested, the MAH has updated the PIL with the changes approved during this variation procedure.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The member states, on the basis of the data submitted, considered that Quetiapine XR AstraZeneca 50 mg, 150 mg, 200 mg, 300 mg and 400 mg, prolonged-release tablets demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

Since the submitted quality, non-clinical and clinical parts of the dossier are identical to the already approved dossier for Seroquel XR (NL/H/0156/008-012), these are acceptable. The critical questions on clinical aspect have been sufficiently addressed.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with the product information of Seroquel immediate-release and XR tablets.

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 that a favourable safety and efficacy profile has been demonstrated for Quetiapine XR AstraZeneca 50 mg, 150 mg, 200 mg, 300 mg and 400 mg, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 11 October 2010. Quetiapine XR AstraZeneca 50 mg, 150 mg, 200 mg, 300 mg and 400 mg, prolonged-release tablets were authorised in the Netherlands on 3 November 2010.

A European harmonised birth date has been allocated (31 July 1997) and subsequently the first data lock point for quetiapine is 31 July 2011. The PSUR cycle is one-yearly.

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

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

Clinical aspects

- The MAH committed to collect additional information about patients lost to follow up (vital status of these patients and the cause of death, if applicable) within the studies when possible.
- The MAH committed to conduct a PASS Study in France in patients with bipolar disorder, subject to post-approval discussions with the competent authority on the appropriate design and associated feasibility.
- The MAH committed to conduct a study of Drug Utilisation in France. In accordance with Volume 9A Notice to Applicants, the design of this study will be discussed and agreed with the French Competent Authority prior to commencement.
- The MAH committed to distribute educational materials to all relevant physicians in France. The format of the educational material will be discussed and agreed with the French Competent Authority prior to launch.

Product information - SPC

- The MAH committed to keep the product information from this DCP in line with the product information of the MRP license of Seroquel XR (with the exception of differences agreed during the current procedure.)

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
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
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