PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Quetiapine Sandoz retard 200 mg, 300 mg and 400 mg,
prolonged-release tablets
Sandoz B.V., the Netherlands

quetiapine (as hemifumarate)

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/2140/001-003/DC
Registration number in the Netherlands: RVG 108460, 108466-108467

5 June 2012

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: 21 May 2012
Concerned Member States: Decentralised procedure with DE, ES, IT, UK
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

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 Sandoz retard 200 mg, 300 mg and 400 mg, prolonged-release tablets from Sandoz B.V. The date of authorisation was on 21 May 2012 in the Netherlands.

The product is indicated for

- Treatment of schizophrenia, including:
  - Preventing relapse in stable schizophrenic patients who have been maintained on quetiapine (see section 5.1 of the approved SPC).
- 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 (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 (5HT₂) and dopamine D₁- and D₂- receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT₂ relative to D₂- 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 α₁ receptors, with a lower affinity at adrenergic α₂ and serotonin 5HT₁A receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Seroquel XR 200 mg, 300 mg and 400 mg, prolonged-release tablets (NL License RVG 34626-32628) which has been registered in the Netherlands by AstraZeneca B.V. since 21 August 2007. A number of EU countries recognised the marketing authorisation through procedure NL/H/0156/009-011/MR. The very first marketing authorisation for Seroquel 200 mg immediate-release tablets was obtained in 1997 in the UK. In addition, reference is made to Seroquel XR authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. 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 reference product. To this end the MAH has submitted four bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product. One study was conducted with the 200 mg product under fasted conditions versus the UK innovator product Seroquel XL 200 mg, and two fed study were performed with the innovator Seroquel XR 200 mg as registered in the Netherlands. The fourth multiple dose study compared the 400 mg strength with Seroquel XR 400 mg prolonged-release tablets,
also obtained from the Netherlands. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

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 hemifumarate, an established active substance for which a draft monograph in the European Pharmacopoeia (Ph.Eur.*) is available. It is a white to off-white powder, which is soluble in dimethylformamide and in glacial acetic acid, and sparingly soluble in methanol. Quetiapine hemifumarate exhibits polymorphism. Form I is used, which is characterized by an X-ray powder diffraction.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
A brief flow diagram of the synthetic route and synthesis narrative has been provided. The process is described in three stages. No potential class I solvents are used. Sufficient data have been provided on starting materials, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The control tests and specifications for drug substance product are adequately drawn up. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 production-scale batches stored at 25°C/60%RH (24 months) and at 40°C/75%RH (6 months) in the proposed market packaging. Additional long-term data to 18 months on a fourth batch and 9 months on a fifth batch has also been provided. All results comply with specification. Based on these data, a retest period of 5 years was approved.

* 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 Sandoz retard 200 mg is a yellow coloured, round shaped, biconvex film-coated tablet, debossed with ‘I2’ on one side and plain on the other.

Quetiapine Sandoz retard 300 mg is a light yellow coloured, round shaped, biconvex film-coated tablet, debossed with ‘Q300’ on one side and plain on the other.

Quetiapine Sandoz retard 400 mg is white coloured, round shaped, biconvex, film-coated tablet, debossed with ‘I4’ on one side and plain on the other.

The prolonged-release tablets are packed in PVC/PVDC-Alu blisters.

The excipients are:
- **Core** - lactose monohydrate, hypromellose, sodium chloride, povidone K-30, talc, magnesium stearate (E572)
- **Coating** - hypromellose 6 cP (E464), titanium dioxide (E171), macrogol (E553b); 200 and 300 mg only: iron oxide yellow (E172).

The different strengths are dose proportional.

**Pharmaceutical development**
The development of the product has been described, the choice of excipients is justified and their functions explained. Formulation development studies were carried out where a formulation which was a scale up/down formulation across the three strengths was developed.

Comparative dissolution studies were carried out on each strength of test and reference. Data obtained in three different media showed comparable dissolution profiles. Also between strengths the dissolution profiles were similar.

**Manufacturing process**
The manufacturing process involves standard steps of sifting, mixing, granulation, wet milling, compression and film-coating. In-process controls are applied to the compression step of the manufacturing process which is considered satisfactory. Process validation was performed on 3 batches of common granulate at the finished product manufacturing site.

A commitment was made to validate the first three consecutive production-scale batches and three production-scale batches of granulate.

**Control of excipients**
All excipients used in the drug product comply with Ph. Eur. specifications, with the exception of the specific coating used for the film-coating. In-house specifications have been provided for these agents. These specifications are acceptable.

**Quality control of drug product**
The product specifications are acceptable and cover the following parameters: average weight of tablets, identification, loss on drying, dissolution, related substances, uniformity of dosage units, assay, residual solvent, microbial examination. Validations of the analytical methods have been presented.

Batch analysis has been performed on three batches of each strength. The batch analysis results show that the finished products meet the specifications proposed.

**Stability of drug product**
Stability data have been provided on three batches of each strength stored at 25°C/60% RH en 40°C/75% RH. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for the drug product are adequately drawn up. The product was demonstrated to be photostable. The proposed shelf-life of 36 months with no special storage conditions for the drug product is considered acceptable on the basis of 24 months long-term stability data. No apparent stability trends were observed.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate, is of bovine origin. The milk is sourced from healthy animals, in the same conditions as those used to collect milk for human consumption. Magnesium stearate is vegetable origin.
Several commitments have been made with regard to the medicinal product; these can be found on page 10 of this report.

II.2 Non-clinical aspects

This product is a generic formulation of Seroquel XR, which is 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
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of quetiapine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Quetiapine is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the test products Quetiapine Sandoz retard 200 mg and 400 mg is compared with the pharmacokinetic profile of the reference product Seroquel XR 200 mg and 400 mg, prolonged-release tablets according the European bioequivalence guideline for preparations with extended release characteristics (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr*).

The following studies have been conducted with the test product:
- Study I – single dose versus Seroquel XL 200 mg (AstraZeneca, UK) under fasted conditions
- Study II – single dose versus Seroquel XR 200 mg (AstraZeneca, NL) under fed conditions
- Study III – multiple dose comparison with Seroquel XR 400 mg (AstraZeneca, NL).

The choice of the reference products
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – 200 mg, single dose, fasted

Design
An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 80 (+ 2 alternate) healthy male subjects with a mean age of 28.1 years. Each subject received a single dose (200 mg) of one of the 2 quetiapine formulations. The tablet was orally administered with 240 ml water after a fasting period of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 24, 36, 48 and 72 hours after administration of the products.

Results
The population included 2 extra subjects to account for possible drop-outs prior to dosing; however these subjects were not needed. One subject withdrew his consent, 2 subjects were withdrawn due to protocol violation (positive alcohol test) and 6 due to adverse events or on medical grounds. Seventy-one subjects completed the study and were included in the statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \(t_{\text{max}}\) (median, range)) of quetiapine under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(\text{AUC}_{0-t}) mg.h/ml</th>
<th>(\text{AUC}_{0-\infty}) mg.h/ml</th>
<th>(C_{\text{max}}) ng/ml</th>
<th>(t_{\text{max}}) h</th>
<th>(t_{1/2}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>3158 ± 1318</td>
<td>3207 ± 1325</td>
<td>268.4 ± 121.1</td>
<td>5.0 (2.0-13.0)</td>
<td>6.2 ± 1.5</td>
</tr>
<tr>
<td>Reference</td>
<td>3355 ± 1447</td>
<td>3408 ± 1447</td>
<td>260.6 ± 101.9</td>
<td>5.0 (2.0-13.0)</td>
<td>6.2 ± 1.6</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.95 (0.89-1.00)</td>
<td>0.95 (0.89-1.00)</td>
<td>1.00 (0.93-1.08)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

\(\text{AUC}_{0-\infty}\) area under the plasma concentration-time curve from time zero to infinity
\(\text{AUC}_{0-t}\) area under the plasma concentration-time curve from time zero to \(t\) hours
\(C_{\text{max}}\) maximum plasma concentration
\(t_{\text{max}}\) time for maximum concentration
\(t_{1/2}\) half-life

\*ln-transformed values

Safety
A total of 18 adverse events (AEs) were reported by 16 subjects during the conduct of the study. Ten AEs were reported in subjects who had received the reference product and 8 were reported in subjects who had received the test product. All AEs reported were mild in nature, and all were followed up till resolution. The causality relationship was judged as possible for 9 adverse events, and as unlikely for 9 adverse events. There were no serious AEs reported during the course of the study. One subject had high total white blood cell count and eosinophilia. He was withdrawn from the study due to an adverse event.

Bioequivalence study II – 200 mg, single dose, fed

Design
An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 64 (+ 2 alternate) healthy male subjects with a mean age of 27.3 years. Each subject received a single dose (200 mg) of one of the 2 quetiapine formulations with 240 mL of water, 30 minutes after a non high-fat breakfast. The nutritional composition of the meal was as follows: 53 kcal protein, 203 kcal of fat and 403 kcal of carbohydrates. The total energy content of the meal was 659 kcal. The subjects had fasted for at least 10 hours before breakfast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 24, 36, 48 and 72 hours after administration of the products.

Results
Two subjects discontinued from the study prior to dosing in Period I and were replaced by two additional subjects. In all, 64 subjects were dosed and 52 subjects completed the clinical phase of the study. The blood samples of these 52 subjects were analysed. Three subjects withdrew their consent and 9 were withdrawn due to adverse events or on medical grounds. The 52 subjects who completed the study were included in the statistical analysis.
Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of quetiapine under fed conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} )</th>
<th>( \text{AUC}_{0-\infty} )</th>
<th>( \text{C}_{\text{max}} )</th>
<th>( t_{\text{max}} ) (h)</th>
<th>( t_{1/2} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>4028 ± 1499</td>
<td>4066 ± 1508</td>
<td>468.9 ± 148.1</td>
<td>5.5 (2.0-12.0)</td>
<td>5.5 ± 1.0</td>
</tr>
<tr>
<td>Reference</td>
<td>4148 ± 1484</td>
<td>4194 ± 1497</td>
<td>412.3 ± 144.8</td>
<td>6.0 (2.0-13.0)</td>
<td>5.9 ± 0.9</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.03 (1.00-1.05)</td>
<td>1.02 (0.99-1.05)</td>
<td>1.15 (1.09-1.21)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td>12.4</td>
<td>12.3</td>
<td>18.3</td>
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</tr>
</tbody>
</table>

\( \text{AUC}_{0-\infty} \): area under the plasma concentration-time curve from time zero to infinity
\( \text{AUC}_{0-t} \): area under the plasma concentration-time curve from time zero to t hours
\( \text{C}_{\text{max}} \): maximum plasma concentration
\( t_{\text{max}} \): time for maximum concentration
\( t_{1/2} \): half-life

*In-transformed values

Safety
A total of 39 AEs were reported by 24 subjects during the conduct of the study. Nineteen adverse events were reported in subjects who had received the reference product and 20 adverse events were reported in subjects who had received the test product. All the adverse events reported were mild in nature. All AEs were followed up till resolution. The causality relationship was judged as possible for 13 adverse events, as unrelated for 1 adverse event and as unlikely for 25 adverse events. There were no serious adverse events reported during the course of the study.

Bioequivalence study III – 400 mg, multiple dose

Design
An open label, multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover, multicentre bioequivalence study was carried out after multiple dose administration in 100 adult schizophrenic patients (65 males, 35 females) stabilized on quetiapine 400 mg per day. Mean age was 32.8 years. Single oral doses of the 400 mg formulations were administered together with 150 mL of water on study days 1 to 8. Cross-over took place at Day 5. The patients had fasted for at least 8 hours prior to drug administration.

Blood samples were withdrawn predose (prior to Dose–01 to Dose–04, and Dose-5 to Dose–08) and at 1.5, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 18 and 24 hours post-dose administration of Dose–04 and Dose–08 (24 hour sample of post-dose administration of Dose–04 was consider as predose sample for Dose-05).

Results
One patient was withdrawn due to emesis and one patient withdrew his informed consent on Day 7. The remaining 98 subjects completed the study and were included in the statistical analysis.

Table 3. Pharmacokinetic parameters in steady-state for quetiapine (non-transformed values; arithmetic mean ± SD), multiple dose

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} )</th>
<th>( \text{C}_{\text{max}} )</th>
<th>( \text{C}_{\text{min}} )</th>
<th>PTF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>9030 ± 4254</td>
<td>808.6 ± 355.6</td>
<td>140.7 ± 104.7</td>
<td>188.9 ± 67.5</td>
</tr>
</tbody>
</table>
Safety
There were a total of 42 adverse events reported by 25 patients. Twelve of these were pre-treatment AEs and 30 AEs occurred post treatment. All the 12 pre-treatment AEs were mild in nature and not related to the study drug. The outcome of 8 of these AEs was unknown, 3 AEs were resolved without any sequelae and 1 AE did not resolve. Of the post-treatment AEs, 28 AEs were mild in nature and 2 AEs were moderate. The causality assessment of 9 AEs was judged as possible, 7 AEs as probable, 9 AEs as unlikely and 5 AEs as not related. The most frequently reported AEs for both study medications were Neutropenia and Pyrexia. All the post-treatment AEs were resolved without any sequelae. No deaths, serious or significant adverse events were reported during the course of the trial.

Conclusion on bioequivalence studies I, II and III
The 90% confidence intervals calculated in study I and II for AUC_{0-t}, AUC_{0-∞} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Bioequivalence was investigated in both fasted and fed state. In study III, bioequivalence has also been demonstrated in steady state following multiple doses. Bioequivalence study II was a fed study using a non-high fat meal. The results indicate that the food effect is comparable between the test and reference product and there is no sign of dose dumping. However, the composition of the meal is not according to the requirements of the Guideline for the Investigation of Bioequivalence. The MAH was therefore asked to justify the choice of a non-high fat meal and discuss the impact of the overall conclusion of bioequivalence.

With their response, the MAH submitted results of a fourth study, which was performed under fed conditions with a high-fat meal. The results are summarized below.

Bioequivalence study IV – 200 mg, single dose, fed

Design
This was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioavailability study in healthy, adult, human male subjects under fed conditions. Quetiapine Sandoz retard 200 mg was compared with Seroquel XL 200 mg (AstraZeneca, UK). A high-fat vegetarian meal was served. As per protocol 64 subjects were dosed in period-I of trial. Out of 64 dosed subjects, 63 subjects completed the clinical phase of the study successfully.

Table 4. Pharmacokinetic parameters in steady-state for quetiapine (non-transformed values; arithmetic mean), single dose, fed conditions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng.h/ml)</th>
<th>AUC_{0-∞} (ng.h/ml)</th>
<th>C_{max} (ng/ml)</th>
<th>t_{max} (h)</th>
<th>t_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>3792.722</td>
<td>3829.424</td>
<td>368.087</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Reference</td>
<td>3752.009</td>
<td>3794.539</td>
<td>428.078</td>
<td>--</td>
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</tr>
</tbody>
</table>

*Ratio (90%) 0.94-1.04 0.95-1.04 1.09-1.24 -- --
Based on the pharmacokinetic parameters of quetiapine under fed conditions, it can be concluded that Quetiapine Sandoz retard 200 mg and Seroquel XL 200 are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. This additional study with a vegetarian high fat diet confirms bioequivalence.

**Extrapolation to different strengths**
The 300 mg tablets are dose proportional with the 200 mg and 400 mg strengths. Sufficient comparative dissolution data have been provided. The results of the bioequivalence studies performed with the 200 and 400 mg tablets therefore apply to the 300 mg strength as well.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

**Risk management plan**
Quetiapine was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of quetiapine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

As a condition of the referral outcome regarding the add-on treatment of major depressive episodes in patients with MDD for the innovator (EMEA/H/A/A-6(13)/1190) it was laid down that for Seroquel an updated RMP had to be submitted, which has only recently been finalised. The outcome thereof will be taken in to account during assessment of the proposal from the MAH. This will be carried out post approval as follow-up measure. The MAH needs to file a separate RMP for this.

**Product information**

**SPC**
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Seroquel.

**Readability test**
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The MAH submitted a user testing report on the proposed PIL which has also been submitted in another DCP, which concluded positively. This report has not been further assessed. Additionally, since the company has copied the Seroquel PIL, separate user testing is not considered necessary.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Quetiapine Sandoz retard 200 mg, 300 mg and 400 mg, prolonged-release tablets have a proven chemical-pharmaceutical quality and are generic forms of Seroquel XR 200 mg, 300 mg and 400 mg. Seroquel XR is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 reference product. 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Quetiapine Sandoz retard 200 mg, 300 mg and 400 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 13 October 2011. Quetiapine Sandoz retard 200 mg, 300 mg and 400 mg, prolonged-release tablets were authorised in the Netherlands on 21 May 2012.

The date for the first renewal will be: 13 October 2016.

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

Quality - medicinal product
- The MAH committed to validate the first three full-scale compression runs of each strength for full conversion of common granules into individual strengths.
- The MAH committed to place the first three maximum scale batches of each strength on stability.
- The MAH committed to re-evaluate total impurities specification limit for shelf life specification after finalization of stability study.

Risk management plan
- The assessment of the RMP of the innovator has only recently been finalised and the outcome thereof will be taken into account during assessment of the proposal from the MAH. The MAH needs to file a separate RMP.
List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
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<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
</tr>
<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
</tr>
<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PIL</td>
<td>Package Leaflet</td>
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<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<td>t&lt;sub&gt;½&lt;/sub&gt;</td>
<td>Half-life</td>
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<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
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