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

EU-procedure number: NL/H/2410/001-003/DC
Registration number in the Netherlands: RVG 110302, 110304 and 110307
14 February 2013

Pharmacotherapeutic group: antipsychotics; diazepines, oxazepines and thiazepines
ATC code: N05AH04
Route of administration: oral
Therapeutic indication: Treatment of schizophrenia and treatment of bipolar disorder; add-on treatment of major depressive episodes in MDD
Prescription status: prescription only
Date of authorisation in NL: 14 September 2012
Concerned Member States: Decentralised procedure with AT, BE, BG, CY, CZ, DE, DK, EL, ES, FI, HU, IS, IE, IT, LT, LU, MT, NO, PL, PT, RO, SE, SI, SK and UK. Withdrawn in FR (at day 106).
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 SR 200 mg, 300 mg and 400 mg, prolonged-release tablets, from Sandoz B.V. The date of authorisation was on 14 September 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 prolonged release.
- 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 prolonged release.

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, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine 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 undesirable effect (EPS) liability of quetiapine compared to typical antipsychotics. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine 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 muscarinic or benzodiazepine receptors.

This decentralised procedure concerns a generic application with reference to the medicinal product Seroquel tablets 200 mg, which was registered on 31 July-1997 in the UK by AstraZeneca. Essential similarity is claimed with Seroquel XR prolonged-release tablets 200 mg, 300 mg and 400 mg (NL License RVG 34626-34628). These products have been registered through MRP NL/H/0156/009-011 since 2007. In addition, reference is made to Seroquel 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 performed bioequivalence studies under fed state (non high-fat diet) with Seroquel XR 200 mg, registered in the Netherlands, under fed state (high-fat diet) versus Seroquel XR 200 mg from the Dutch market, under steady state with Seroquel XR 400 mg, also obtained from the Netherlands and under fasting state with Seroquel XL 200 mg, registered in the UK.

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 however not described in the European Pharmacopoeia (Ph.Eur.*) or any other pharmacopoeia. The active substance is a white to off-white crystalline powder which is soluble in dimethylformamide and glacial acetic acid and sparingly soluble in methanol. The polymorphic form produced is form I.

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
The synthesis processes, starting materials, solvents and reagents have been included in the description. The drug substance is formed in a four step process. This manufacturing process is adequately described. The active substance has been adequately characterized. No class 1 organic has been used in the manufacturing process.

Quality control of drug substance
The active substance specification and requirements are considered adequate to control the quality and are in line with general requirements and related substances limits are in line with ICH Guideline limits for drug substances. A draft monograph for Quetiapine fumarate has been described in Pharmeuropa 22.1, January 2010. The limits for specified impurities and heavy metals are more stringent than those described in the draft monograph, while the limits for total impurities and loss on drying are wider. Batch analytical data demonstrating compliance with this specification have been provided for six batches. Adequate information has been presented on the container closure systems.

Stability of drug substance
Stability data on the active substance have been provided for 3 production-scale batches, stored at 25°C/60%RH for 48 months and at 40°C/75%RH for 6 months in the proposed market packaging. Additional long term data were also provided for up to 48 months. One larger batch was placed on stability as well, but only initial data was presented. All results comply with the specification. No increase in impurities was seen. No significant changes in any parameters were observed. The proposed retest period of 5 years is justified.

* 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 SR 200 mg are yellow coloured, round shaped, biconvex film coated tablets, debossed with ‘I2’ on one side and plain on other.
Quetiapine Sandoz SR 300 mg are light yellow coloured, round shaped, biconvex film coated tablets, debossed with ‘Q300’ on one side and plain on other.
Quetiapine Sandoz SR 400 mg are white coloured, round shaped, biconvex, film coated tablets debossed with ‘I4’ on one side and plain on other.

The 200 mg, 300 mg and 400 mg prolonged-release tablets are dose proportional.

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

The excipients are:
Core: Lactose monohydrate, Hypromellose, Sodium chloride, Povidone K-30, Talc and Magnesium stearate (E470b).
Coating 200 mg: Hypromellose (E464), Titanium dioxide (E171), Macrogol 6000 and Iron oxide yellow (E172).
Coating 300 mg: Hypromellose (E464), Titanium dioxide (E171), Macrogol 6000 and Iron oxide yellow (E172).
Coating 400 mg: Hypromellose (E464), Titanium dioxide (E171) and Macrogol 6000.

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. The initial studies were carried out on the highest strength tablet, 400 mg and scaled accordingly for the remaining strengths.
Dissolution was compared with reference product 400 mg tablets in water media and results are presented. The dissolution method development has been adequately described and the discriminating nature of the method has been demonstrated. The biowaiver for the 300 mg strength has been supported by comparative dissolution studies. Except for the 200 mg strength of the test product compared to the 300 mg and 400 mg of the test product in differential pH media, all profiles demonstrate similarity. The dissimilar results were adequately discussed and justified to be due to properties of the drug substance, rather than the formulation of the drug product.

Manufacturing process
Manufacturing process is a standard tableting process of sifting, mixing, granulation, wet milling, compression and film-coating. Optimisation of blend time assessed by blend uniformity was considered as appropriate. Resistance to crushing and compression speed were also assessed. Process validation was performed on 3 pilot batches for both granulate and each strength of the finished product.

Control of excipients
All excipients used in the drug product with the exception of the specific coating used for the film coating are of Ph. Eur. grade. Excipient specifications are stated as complying with current monograph requirements and are supported by certificates of analysis from both suppliers and the finished product manufacturer. An in-house specification has been provided for all the Opadry colourants which are used in the film-coating solution. Satisfactory certificates of analysis are provided for each of the Opadry colours from the finished product manufacturer.
Quality control of drug product
The product specification includes tests for appearance, average weight of tablets, identification by HPLC and UV, identification of the colorants, loss on drying, dissolution, related substances, uniformity of dosage units, assay, residual solvent and microbiology.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 3 batches of each strength have been provided, demonstrating compliance with the specification.
Adequate information has been presented on the container closure systems.

Stability of drug product
Stability data on the product has been provided for three batches of each strength under long term storage conditions (18 months) and accelerated conditions (6 months). The product remains stable in the proposed packaging under all storage conditions and no trends are apparent from the data, with all specification parameters remaining within set limits. No fall in assay or rise in impurities is observed. Photostability has been demonstrated. A shelf-life of 30 months can be granted without any special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Statements confirming the absence of TSE risk have been provided from all excipient suppliers and are accepted. Magnesium stearate is vegetable origin. Lactose monohydrate is of bovine origin, as per the statement included in the declaration. The milk is sourced from healthy animals, in the same conditions as those used to collect milk for human consumption.

II.2 Non-clinical aspects
This product is a generic formulation of Seroquel, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
A short statement on the environmental risk has been provided, stating that 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 four bioequivalence studies in which the pharmacokinetic profile of the test product Quetiapine Sandoz SR 200 mg and 400 mg, prolonged-release tablets is compared with the pharmacokinetic profile of the reference product Seroquel XR prolonged release tablets 200 mg and 400 mg. The MAH conducted 4 bioequivalence studies: one in fasted state, two in fed state (high fat and non high-fat diet) and one in steady-state according the European bioequivalence guideline for preparations with extended release characteristics (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr*).

The reference product used in the fasted and the high fat study was obtained from the UK, in the remaining two studies the Dutch reference product was used.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

Study I, fasted conditions:
An open label, balanced, randomized, two-treatment, two period, two-sequence, single dose, cross-over, comparative oral bioavailability study of two formulations of quetiapine extended release (ER) tablets 200 mg in healthy normal, adult, human male subjects under fasting condition. Single oral doses of the assigned formulation were administered with 240 ml of water. The subjects had fasted for at least 10 hours before drug administration. Blood samples were drawn 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. The wash-out period between study periods was 7 days. The study is performed with the lowest strength of 200 mg, for reasons of intolerance. This is in line with the recommended posology of a low starting dose and gradual up-titration. The study design is acceptable. GCP statement has been provided.

82 healthy male subjects with a mean age of 28.1 years and a mean BMI of 21.37 were included in the study. The population included 2 extra subjects to account for possible drop-outs; however these subjects were not needed. 71 subjects completed the study and were included in the statistical analysis. 1 subject withdraw his informed consent, 2 subjects were withdrawn due to protocol violation (positive alcohol breath test) and 6 due to adverse events or on medical grounds. There were no serious adverse events reported during the course of the study.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_max (median, range)) of quetiapine under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_0-t</th>
<th>AUC_0-∞</th>
<th>C_max</th>
<th>t_max</th>
<th>t_1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>3158 ± 1318</td>
<td>3207± 1325</td>
<td>268 ± 121</td>
<td>5 (2 – 13)</td>
<td>6.2 ± 1.5</td>
</tr>
<tr>
<td>Reference</td>
<td>3355 ± 1447</td>
<td>3408 ± 1447</td>
<td>261 ± 101</td>
<td>5 (2 – 13)</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>
<tr>
<td>CV (%)</td>
<td>21</td>
<td>20</td>
<td>27</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*AUC_0-t area under the plasma concentration-time curve from time zero to t hours
AUC_0-∞ area under the plasma concentration-time curve from time zero to infinity
C_max maximum plasma concentration
C_v time for maximum concentration

Study II, fed conditions (non high-fat diet)
An open label, balanced, randomized, two-treatment, two period, two-sequence, single dose, cross-over, comparative oral bioavailability study of two formulations of quetiapine extended release (ER) tablets 200 mg in healthy normal, adult, human male subjects under fed condition (non high-fat diet). Single oral doses of the assigned formulation were administered together 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. Blood samples were drawn 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. The wash-out period between study periods was 7 days.
66 healthy male subjects (including 2 additional subjects as alternate in case of drop outs) with a mean age of 27.3 years and a mean BMI of 20.89 checked-in for the study. Two subjects discontinued from the study prior to dosing in Period-I and were replaced by the two additional subjects. 64 subjects were dosed and 52 subjects completed the clinical phase of the study. The blood samples of these 52 subjects were analysed. 3 subjects withdrew their informed consent and 9 were withdrawn due to adverse events or on medical grounds. There were no serious adverse events reported during the course of the study.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ (median, range)) of quetiapine under fed conditions (non high-fat diet).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-\text{t}}$ (ng.h/ml)</th>
<th>$\text{AUC}_{0-\infty}$ (ng.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>4028 ± 1499</td>
<td>4063 ± 1508</td>
<td>469 ± 148</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 ± 145</td>
<td>6.0 (2.0-13.0)</td>
<td>5.9 ± 0.9</td>
</tr>
</tbody>
</table>

$^*\text{Ratio (90\% CI)}$

<table>
<thead>
<tr>
<th>$\text{AUC}_{0-\infty}$</th>
<th>$\text{AUC}_{0-\text{t}}$</th>
<th>$C_{\text{max}}$</th>
<th>$t_{\text{max}}$ (h)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>area under the plasma concentration-time curve from time zero to infinity</td>
<td>area under the plasma concentration-time curve from time zero to t hours</td>
<td>maximum plasma concentration time for maximum concentration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ (median, range)) of quetiapine under fed conditions (high fat diet).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-\text{t}}$ (ng.h/ml)</th>
<th>$\text{AUC}_{0-\infty}$ (ng.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>4150 ± 2127</td>
<td>4191± 2138</td>
<td>466 ± 212</td>
<td>5.5 (2 – 14)</td>
<td>5.8 ± 1.1</td>
</tr>
<tr>
<td>Reference</td>
<td>4185 ± 2152</td>
<td>4220 ± 2157</td>
<td>398 ± 168</td>
<td>5.5 (3.5 – 13)</td>
<td>5.9 ± 1.5</td>
</tr>
</tbody>
</table>

$^*\text{Ratio (90\% CI)}$

<table>
<thead>
<tr>
<th>$\text{AUC}_{0-\infty}$</th>
<th>$\text{AUC}_{0-\text{t}}$</th>
<th>$C_{\text{max}}$</th>
<th>$t_{\text{max}}$ (h)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln(transformed values)</td>
<td>ln(transformed values)</td>
<td>ln(transformed values)</td>
<td>ln(transformed values)</td>
<td>ln(transformed values)</td>
</tr>
</tbody>
</table>

Study III, fed conditions (high-fat diet)
An open label, balanced, randomized, two-treatment, two period, two-sequence, single dose, cross over, comparative oral bioavailability study of two formulations of quetiapine extended release (ER) tablets 200mg in healthy normal, adult, human male subjects under fed condition (high-fat diet). After an overnight fast of at least 10 hours, the subjects were served a standardized high–fat, high-calorie vegetarian breakfast, which they consumed within 30 minutes. Subjects received a single oral dose of the assigned formulation 30 minutes after consuming breakfast. The duration of the study treatment was 17 days, including a washout period of 12 days between treatment periods.

Sixty-four (64) Asian male aged 20 to 44 years with a BMI of 19– 25 kg/m$^2$ were randomised and dosed. Sixty-three (63) subjects completed both study periods, as one subject was withdrawn on the day of dosing in Period II due to emesis. There were no serious adverse events reported during the course of the study.
Study IV, steady state

An open label, balanced, randomized, two-treatment, two period, two-sequence, cross-over, multi-centric experimental comparative evaluation of two formulations of quetiapine extended release tablets 400mg under fasting conditions after multiple dose administration at steady state in adult schizophrenic patients stabilized on Quetiapine 400 mg per day.

Single oral doses of the assigned formulation 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. The venous blood samples were drawn pre-dose (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 considered pre-dose sample for Dose-05).

Of the 100 patients enrolled and treated, 65 (65%) were males and 35 (35%) were females. The mean age was 32.8 years and the mean BMI was 22.42. One patient was withdrawn due to emesis and one patient withdrew his informed consent. No deaths, serious or significant adverse events were reported during the course of the trial.

Table 4. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUCₜ ng/ml/h</th>
<th>Cₘₐₓ ng/ml</th>
<th>Cₘᵢₙ,ss ng/ml</th>
<th>PTF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>9030 ± 4254</td>
<td>809 ± 356</td>
<td>141 ± 105</td>
<td>189 ± 68</td>
</tr>
<tr>
<td>Reference</td>
<td>9200 ± 3929</td>
<td>762 ± 286</td>
<td>158 ± 111</td>
<td>168 ± 49</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.98 (0.93 – 1.02)</td>
<td>1.05 (1.00 – 1.11)</td>
<td>0.88 (0.81 – 0.95)</td>
<td>-</td>
</tr>
<tr>
<td>CV (%)</td>
<td>19</td>
<td>23</td>
<td>35</td>
<td>-</td>
</tr>
</tbody>
</table>

The 90% confidence intervals calculated for AUC₀-t, AUC₀-∞ and Cₘₐₓ are in agreement with those calculated by the MAH and for the 200 mg formulation (fasting and fed state) and for the 400 mg formulation (steady state) the mean ratios of all the primary pharmacokinetic parameters are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of quetiapine it can be concluded that Quetiapine Sandoz SR 200 mg an 400 mg, prolonged-release tablets and the Seroquel XR 200 mg and 400 mg prolonged-release tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

**Biowaiver**

A biowaiver for the 300 mg strength has been justified based on the following:
- The fasted and fed studies performed with the 200 mg strength and steady state study performed with the 400 mg strength provide a good estimate of pharmacokinetic difference with 300 mg.
- Considering the comparable dissolution profile in multimedia between respective strengths of test versus reference product and the test product used in the bioequivalence study versus the additional strength for the biowaiver
- All three strengths are manufactured in the same facility using the same manufacturing process.
- The qualitative composition of all the three strengths is the same.
- The formulation of all three strengths is dose proportional.
- In-vitro dissolution profiles are comparable between the strengths used in the bioequivalence study and the 300 mg strength.
- Pharmacokinetics across the strengths is linear.

Risk management plan
In accordance with the EU-RMP guideline, a risk management plan with enhanced risk minimisation activities is implemented for the reference medicinal product for physicians and other healthcare providers, intended to address risks of particular interest in the bipolar depression population (specifically extrapyramidal symptoms and somnolence/sedation) and monitoring of metabolic parameters. Therefore the following commitments were made:
1. The following issues will be closely monitored and specifically reported upon in the PSURs:
   - Hyperglycaemia and diabetes mellitus, hypothyroidism, increased blood pressure in paediatric population;
   - Cerebrovascular adverse events (CVAEs) in elderly and in non-elderly, serotonin syndrome (SS), agranulocytosis, QTc prolongation and Torsade de pointes, sudden death, myocarditis, ischaemic heart disease, potential consequences of metabolic syndrome/ metabolic risk factors, cataracts, aggression/ agitation, venous thromboembolism and pulmonary embolism, suicide and suicidality, pancreatitis, rhabdomyolysis, pneumonia itself as well as a consequence of other events (e.g. dysphagia, choking and aspiration), off-label use and misdosing potential, elderly patients;
   - Pregnant or lactating women, renally impaired patients, patients with hepatic impairment, patients of different or certain ethnic or racial origin, patient on concomitant cardiovascular medication, patients on concomitant valproic acid, long-term exposure, malignancies.
2. The SmPC for the product will follow, and be kept in line, with the SmPC of the innovator.
3. The MAH will follow, where appropriate, the risk minimization activities of the innovator, e.g. participate in DHPCs where needed, produce and distribute educational material for patients and physicians when applicable, etc. Currently no educational material/ additional risk minimization measures need to be issued by the MAH.

Product information

SmPC
The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Seroquel XR marketed by AstraZeneca.

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 test consisted two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The questions sufficiently focused on the ability to find and understand the information and use the product appropriately. > 90% of the participants were able to both find and understand the information. The number of wrong answers given is acceptable (1.79%). The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Quetiapine Sandoz SR 200 mg, 300 mg and 400 mg, prolonged-release tablets have a proven chemical-pharmaceutical quality and are generic forms of Seroquel XR tablets. 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 SmPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other quetiapine containing products.

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 essential similarity has been demonstrated for Quetiapine Sandoz SR 200 mg, 300 mg and 400 mg, prolonged-release tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 21 August 2012. Quetiapine Sandoz SR 200 mg, 300 mg and 400 mg, prolonged-release tablets were authorised in the Netherlands on 14 September 2012.

The date for the first renewal will be: 21 August 2017.

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

Pharmacovigilance:

RMP:
1. The following issues will be closely monitored and specifically reported upon in the PSURs:
   - Hyperglycaemia and diabetes mellitus, hypothyroidism, increased blood pressure in paediatric population;
   - Cerebrovascular adverse events (CVAEs) in elderly and in non-elderly, serotonin syndrome (SS), agranulocytosis, QTc prolongation and Torsade de pointes, sudden death, myocarditis, ischaemic heart disease, potential consequences of metabolic syndrome/ metabolic risk factors, cataracts, aggression/ agitation, venous thromboembolism and pulmonary embolism, suicide and suicidality, pancreatitis, rhabdomyolysis, pneumonia itself as well as a consequence of other events (eg dysphagia, choking and aspiration), off-label use and misdosing potential, use in elderly patients;
   - Pregnant or lactating women, renally impaired patients, patients with hepatic impairment, patients of different or certain ethnic or racial origin, patient on concomitant cardiovascular medication, patients on concomitant valproic acid, long-term exposure, malignancies.
2. The SmPC for the product will follow, and be kept in line, with the SmPC of the innovator.
3. The MAH will follow, where appropriate, the risk minimization activities of the innovator, e.g. participate in DHPCs where needed, produce and distribute educational material for patients and physicians when applicable, etc. Currently no educational material/ additional risk minimization measures need to be issued by the MAH.
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\text{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\frac{1}{2}  Half-life
t_{\text{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

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<th>Scope</th>
<th>Procedure number</th>
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<th>Date of start of the procedure</th>
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<th>Approval/ non approval</th>
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