IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Quetiapine Rowex 50 mg Prolonged-release tablets
Quetiapine
PA0711/231/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number NL/H/2565/001 with the NL as RMS. The responsibility of RMS was transferred to Ireland on 11/11/2020 under procedure number IE/H/1156/001/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0711/231/001
Marketing Authorisation Holder: Sandoz

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The NL public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Quetiapine Sandoz 50 mg prolonged release tablets, from Sandoz B.V. The date of authorisation was on 1 August 2013 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 50mg, 200 mg, 300 mg and 400 mg (NL License RVG 34625-34628). 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 fasting condition with Seroquel XR 50mg and XR 200 mg, under fed state (high-fat diet) with Seroquel XR 200 mg, registered in the Netherlands, under fed state (non-high-fat diet) versus Seroquel XR 50mg and Seroquel XR 200 mg from the Dutch market, under steady state with Seroquel XR 400 mg, 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. 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. A draft monograph is described in Pharmaeuropa 22.1 (January 2010). The active substance is a white to off white powder which is soluble in dimethylformamide and glacial acetic acid, 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 manufacture of quetiapine fumarate consists of three steps. The last step of the synthesis is the salt formation and purification. No class 1 organic solvents or heavy metal catalysts are used.
The proposed starting materials are acceptable. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three full batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). All results comply with the specification limits. No increases are observed with respect to impurities. Based on the stability results provided the proposed shelf life of 60 months without special storage conditions can be granted.

** 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 50 mg arepeach colored, round shaped, biconvex film coatedprolonged release tablets, debossed with 'Q50' on one side and plain on the other. The diameter of the tablet is 11.2 ± 0.2 mm.

The core tablets of the 200 mg, 300 mg and 400 mg strength are fully dose proportional. The 50 mg is not dose proportional to the other strengths.

The 50 mg strength tablets are either packed in white opaque PVC/PVDC-Alu blister packs or OPA/Alu/PVC-Alu blister packs.
The 200 mg, 300 mg and 400 mg tablets are packed in white opaque PVC/PVDC-Alu blister packs.

The excipients are:
Tablet core 50 mg tablets: lactose monohydrate, hypromellose (K4M and K100 Premium LV CR), sodium chloride, povidone K-30, silicified microcrystalline cellulose (cellulose microcrystalline and silica colloidal anhydrous), talc, magnesium stearate (E470b).
Tablet core 200 mg, 300 mg and 400 mg: lactose monohydrate, hypromellose (K4M), sodium chloride, povidone K-30, talc, magnesium stearate (E470b).

Coating 50 mg: opadry II 85F540003 pink: poly (vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), iron oxide red (E172), iron oxide yellow (E172).
Coating 200 mg: opadry 03B52117 yellow: hypromellose 6 cP (E464), titanium dioxide (E171), macrogol 400 (E1521), iron oxide yellow (E172).
Coating 300 mg: opadry 03B82929 yellow: hypromellose 6 cP (E464), titanium dioxide (E171), macrogol 400 (E1521), iron oxide yellow (E172).
Coating 400 mg: opadry 03B58900 white: hypromellose 6 cP (E464), titanium dioxide (E171), macrogol 400 (E1521).

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the originator product, formulation trials and comparative dissolution studies.
Bioequivalence studies were performed with full scale batches of the 50 mg, 200 mg and 400 mg drug product. The batches used in the bioequivalence studies have the same composition and are manufactured in the same way as the future commercial batches. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into the following steps: pre-blending, wet granulation, drying, sifting, blending, compression, film-coating and packaging.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches of 50 mg, 200 mg, 300 mg and 400 mg tablets. For the 50 mg tablets process validation data has been provided on three batches of the smallest production scale. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with relevant Ph.Eur. or USP NF requirements. These specifications are acceptable.
The analytical methods used for the Opadry powders have been adequately described. Since the methods used are either compendial or simple of nature, no validation is considered necessary.

Quality control of drug product

The product specification includes tests for appearance, average weight, identity, loss on drying, dissolution, related substances, uniformity of dosage units, assay, residual solvents and microbial quality. The release and shelf-life requirements/limits are identical, except for loss on drying for the 50 mg tablets. The drug product specification is acceptable.

The analytical methods been adequately described and validated.

Batch analytical data from the proposed production site have been provided on three full scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided of three full scale batches of 200 mg, 300 mg and 400 mg tablets stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). Furthermore, stability data has been provided of three full scale batches of 50 mg tablets stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored the proposed market packaging.

Increases in loss off drying were observed in the PVC-PVDC/Al blister for all strengths at both conditions. However, the increases were more pronounced in the 50 mg strength and at accelerated conditions. All other parameters examined, remained relatively stable throughout the test periods for all strengths at both conditions and within specification (with the exception of some analytical variance). Photostability studies were performed on crushed tablets which is acceptable, since this condition is considered worse than the intact tablet. The finished product is considered photostable

Based on the provided stability data a shelf life of 36 months for the 200 mg, 300 mg and 400 mg tablets and a shelf life of 30 months for the 50 mg tablets can be granted. No special storage conditions are required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the materials used in the manufacture of quetiapine prolonged release tablets are of animal or human origin, except for lactose monohydrate.

The manufacturer of lactose monohydrate has confirmed that it does not have potential risk for TSE/BSE and it is derived from milk, sourced from healthy animals in the same conditions as milk collected for human consumption and is prepared in accordance with the relevant requirements laid down in Note for Guidance EMEA/410/01, rev2.

III. 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

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 fumarate 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.

IV. CLINICAL ASPECTS

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

For this generic application, the MAH has submitted 7 bioequivalence studies in which the pharmacokinetic profile of the test product Quetiapine Sandoz 50 mg, prolonged-release tablets is compared with the pharmacokinetic profile of the reference product Seroquel XR prolonged release tablets 50 mg, 200 mg and 400 mg. The MAH conducted 7 bioequivalence studies: two under fasted conditions, three in fed state (high fat and non high-fat diet) and two in steady-state according to the European bioequivalence guideline for preparations with extended release characteristics (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr* and CPMP/EWP/280/96 Corr *).

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.

Study I, fasted conditions (200 mg)

Design

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioequivalence study was carried out under fasted conditions in 82 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 fumarate formulations. The tablet was orally administered with 240 ml water after a fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected 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 of the products.

The study design is acceptable. A GCP statement has been provided.

Analytical/statistical methods

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

Results

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. The population included 2 extra subjects to account for possible drop-outs; however these subjects were not needed.

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

Treatment N=71	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3158 ± 1318	3207± 1325	268 ± 121	5 (2 – 13)	6.2 ± 1.5
Reference	3355 ± 1447	3408 ± 1447	261 ± 101	5 (2 – 13)	6.2 ± 1.6
***Ratio (90% CI)**	0.95 (0.89 – 1.00)	0.95 (0.89 – 1.00)	1.00 (0.93 – 1.08)	-	-
CV (%)	21	20	27	-	-
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

Safety

A total of 18 adverse events were reported by 16 subjects during the conduct of the study. 10 adverse events were reported in subjects who had received the reference product and 8 adverse events were reported in subjects who had received the test product. All the adverse events reported were mild in nature. All the adverse events were followed up till resolution. The causality relationship was judged as possible for 9 adverse events, as and as unlikely for 9 adverse events. There were no

serious adverse events 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.

Study II, fed conditions – non-fat diet (200 mg)

Design

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioequivalence study was carried out under fed conditions in 66 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 fumarate formulations. The tablet was orally administered with 240 ml 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 two dosing periods, separated by a washout period of 7 days.

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 study design is acceptable. A GCP statement has been provided.

Analytical/statistical methods

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

Results

Two subjects (discontinued from the study prior to dosing in Period-I and were replaced by the 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. 3 subjects withdrew their informed consent and 9 were withdrawn due to adverse events or on medical grounds.

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

Treatment N=52	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4028 ± 1499	4062 ± 1508	469 ± 148	5.5 (2.0-12.0)	5.5 ± 1.0
Reference	4148 ± 1484	4194 ± 1497	412 ± 145	6.0 (2.0-13.0)	5.9 ± 0.9
***Ratio (90% CI)**	0.97 (0.93-1.01)	0.97 (0.93-1.01)	1.16 (1.09-1.23)	-	-
CV (%)	12	12	18	-	-
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

Safety

A total of 39 adverse events were reported by 24 subjects during the conduct of the study. 19 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 the adverse events 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.

Study III, fed conditions – high-fat diet (200 mg)

Design

An open label, balanced, randomized, two-treatment, two period, two-sequence, single dose, cross-over, comparative oral bioequivalence study was carried out under fed conditions in 64 healthy Asian male subjects, aged 20 - 44 years. 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 dose (200 mg) of one of the 2 quetiapine fumarate formulations 30 minutes after consuming breakfast. There were two dosing periods, separated by a washout period of 12 days.

The study design is acceptable. A GCP statement has been provided.

Analytical/statistical methods

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

Results

Sixty-three subjects completed the study, as one subject was withdrawn on the day of dosing in Period II due to emesis.

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

Treatment N=63	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4150 ± 2127	4191± 2138	466 ± 212	5.5 (2 – 14)	5.8 ± 1.2
Reference	4185 ± 2152	4220 ± 2157	398 ± 168	5.5 (3.5 – 13)	5.9 ± 1.5
***Ratio (90% CI)**	0.99 (0.94 – 1.04)	0.99 (0.95 – 1.04)	1.16 (1.10 – 1.24)	-	-
CV (%)	16 (22)	16 (17)	21 (17)	-	-
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

Safety

Three adverse events were reported during the conduct of the trial. Two of the AEs were judged to be unlikely and one AE was possibly related to the study drug. There were no deaths or serious / significant adverse event reported in the study. There were no clinically significant findings in the vital signs assessment or in the laboratory tests for majority of the subjects.

Study IV, steady state (400 mg)

Design

An open label, balanced, randomized, two treatment, two-period, two-sequence, crossover, multicenter experimental comparative evaluation of two formulations of Quetiapine extended release tablets 400 mg under fasting conditions after multiple dose administration at steady state in 100 adult schizophrenic patients, 65 male and 35 female with a mean age of 32.8, stabilized on Quetiapine 400 mg per day.

Single oral doses (400 mg) 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.

Blood samples were drawn pre-dose and at 1.5, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 18 and 24 hours after administration.

The study design is acceptable. A GCP statement has been provided.

Analytical/statistical methods

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

Results

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

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

Treatment **N=98**	**AUC_t** **ng/ml/h**	**C_{max}** **ng/ml**	**C_{min}** **ng/ml**	**PTF%** **%**
Test	9030 ± 4254	809 ± 356	141 ± 105	189 ± 68
Reference	9200 ± 3929	762 ± 286	158 ± 111	168 ± 49
***Ratio** **(90% CI)**	0.98 (0.94 – 1.02)	1.05 (1.00 – 1.11)	0.88 (0.81 – 0.95)	-
CV (%)	19	23	35	-
AUC_t area under the plasma concentration-time curve over the dosing interval **C_{max}** maximum plasma concentration **C_{min}** minimum plasma concentration **PTF%** fluctuation index				

Safety

There were a total of 42 adverse events reported by 25 patients. 12 AEs were pre-treatment AEs and 30 AEs were post-treatment AEs.

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, 03 AEs were resolved without any sequeale and 01 AE did not resolve. Of the post-treatment AEs, 28 AEs were mild in nature and 02 AEs were moderate. The causality assessment of 09 AEs was judged as possible, 07 AEs as probable, 09 AEs as unlikely and 05 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 sequeale. No deaths, serious or significant adverse events were reported during the course of the trial.

Study V, fasted conditions (50 mg)

Design

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioequivalence study was carried out under fasted conditions in 56 healthy non-smoking, adult subjects, aged 18 - 55 years. Each subject received a single dose (50 mg) of one of the 2 quetiapine fumarate formulations. The tablet was orally administered with 240 ml water after a fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected 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, 12, 13, 14, 16, 20, 24 and 36 hours after administration of the products.

The study design is acceptable. A GCP statement has been provided.

Analytical/statistical methods

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

Results

54 subjects completed the study and were included in the statistical analysis. Two subjects were withdrawn from the study on the grounds of protocol deviation as both of them were found positive in breath test for alcohol consumption on the day of check in for Period-II.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of quetiapine fumarate under fasted conditions.

Treatment N=54	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1016 ± 438	1102± 473	70 ± 29	5 (1 – 16)	7 ± 3.3
Reference	1094 ± 459	1156 ± 470	76 ± 34	8 (3 – 14)	6.5 ± 1.7
***Ratio (90% CI)**	0.92 (0.86 – 0.99)	0.95 (0.88 – 1.01)	0.93 (0.85 – 1.01)	-	-
CV (%)	22.6	22.3	26.8	-	-
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

Safety

No adverse events were reported in the study.

Study VI, fed conditions – high-fat diet (50 mg)

Design

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioequivalence study was carried out under fed conditions in 80 healthy, non-smoking, adult male subjects, aged 18 - 55 years. 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 dose (50 mg) of one of the 2 quetiapine fumarate formulations together with 240 mL of water 30 minutes after consuming breakfast. There were two dosing periods, separated by a washout period of 7 days.

The study design is acceptable. A GCP statement has been provided.

Analytical/statistical methods

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

Results

In total 75 subjects completed the study and were included in the analyses, 5 subjects were withdrawn: One subject was found positive in the breath test for alcohol consumption on the check-in day of Period-II; hence the subject was withdrawn from the study on grounds of Protocol deviation. One subject was withdrawn from the study on medical grounds in Period-II. Two subjects were withdrawn from the study on grounds of emesis in Period-II. One subject discontinued from the study on his own accord in Period-II due to his personal reasons.

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of quetiapine fumarate under fed conditions.

Treatment N=75	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1295 ± 630	1362 ± 686	132 ± 61	5.55 (3 – 12)	6.3 ± 1.8
Reference	1330 ± 663	1382 ± 677	142 ± 64	6 (3 – 12)	6.1 ± 1.2
***Ratio (90% CI)**	0.97 (0.94 – 1.01)	0.98 (0.94 – 1.02)	0.92 (0.86 – 0.98)	-	-
CV (%)	13.2	14.4	23.6	-	-
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

Safety

Four adverse events were reported by three subjects during the conduct of study. All the four AEs were reported in Period-II of the study. Three AEs were reported after the receipt of Test Product and one adverse event was reported after the receipt of

Reference Product. All the four AEs were mild in nature and were followed –up until resolution. The causality assessment was judged as possibly related for two AEs and unlikely related for the other two AEs to the investigational product administered.
One significant AE was reported during the course of the study: upper respiratory tract infection to one subject in Period-II. The causality assessment of the significant AE was termed as unlikely related to the study drug administered.

Study VII, steady state (50 mg)
Design
An open label, balanced, randomized, two-treatment, two period, two-sequence, cross over, comparative oral bioequivalence study was carried out under fasted conditions in 56 healthy, non-smoking, adult male subjects, aged 18 - 55 years. Single oral doses (50 mg) of the assigned formulation were administered 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. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were drawn pre-dose and (after dose 4) at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 14, 16, 20 and 24 hours after administration.

The study design is acceptable. A GCP statement has been provided.

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

Results
On the day of check-in for Period-I, two subjects informed the study personnel that they did not want to continue further in the study. Hence, the subjects discontinued from the trial on his own accord. They were replaced with two additional subjects. 56 subjects completed the study and were included in the analyses.

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

Treatment N=56	**AUC_t** ng/ml/h	**C_{max}** ng/ml	**C_{min}** ng/ml	**PTF%** %
Test	1025.1 ± 481.6	77.5 ± 40.7	14.7 ± 10.3	151 ± 53.6
Reference	1065.4 ± 430.6	84.8 ± 36.3	16.4 ± 10.9	159.6 ± 57
***Ratio (90% CI)**	0.95 (0.87 – 1.01)	0.89 (0.83 – 0.96)	0.92 (0.81 – 1.05)	-
CV (%)	21	24	42.5	-
AUC_t area under the plasma concentration-time curve over the dosing interval **C_{max}** maximum plasma concentration **C_{min}** minimum plasma concentration **PTF%** fluctuation index				

Safety
No adverse events were reported during the conduct of the trial.

In all studies the 90% confidence intervals calculated for AUC0-t, AUC0-∞ and Cmax are in agreement with those calculated by the MAH and for the 50 mg and 200 mg formulation (fasting and fed state) and for the 50 mg and 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 50mg, prolonged-release tablets and the Seroquel XR 50mg, 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 for 300 mg strength
A biowaiver is granted for the 300 mg strength based on the following:

- Fasted and fed study performed on 200mg strength and steady state study preformed on 400mg strength would give good estimate of PK difference with 300mg.
- Considering the comparable dissolution profile between respective strength of test versus reference product and test product of BE study versus additional strength for biowaiver of test product in multimedia
- All three strengths are manufactured in same facility using same manufacturing process
- The qualitative composition of all the three strengths is same
- The formulation of all the three strengths is dose proportional
- In-vitro dissolution profile is comparable between the strength used in BE study and additional strengths
- Linear pharmacokinetics across the strengths

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 (eg 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

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 MAH submitted a bridging report between the proposed product and Seroquel prolonged release tablets. The applicant reflects on several aspects for bridging with the innovator's patient leaflet including:

- Both 'Parent' and 'Daughter' PILs are similar in content.

- The patient can find and understand key messages of the PIL so that they can use the medicine safely
- Font and font size used in both 'Parent' and 'Daughter' PILs are almost similar.
- Headings and sub-headings including consistency of placement used in both 'Parent' and 'Daughter' PILs are identical.

- PIL dimensions including portrait format of both 'Parent' and 'Daughter' PILs are consider acceptable.
- Colors used in the PILs of 'Parent' and 'Daughter' are in line with EU requirement.
- Layout of critical safely sections mentioned in 'Parent' and 'Daughter' PILs are identical.
- The target patient population will be similar for both 'Parent' and 'Daughter' PILs.
- Same active moiety for both 'Parent' and 'Daughter' PILs.

This bridging statement is considered acceptable and the readability of the PL is therefore considered approvable.

V. OVERALL CONCLUSIONS

Quetiapine Sandoz 50 mg, prolonged release tablets have a proven chemical-pharmaceutical quality and are generic forms of Seroquel XR tablets. Seroquel 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 and are in agreement with other quetiapine fumarate 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 with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 3 July 2013. Quetiapine Sandoz is authorised in the Netherlands on 1 August 2013.

The date for the first renewal will be: 1 August 2018.

There were no post-approval commitments made during the procedure.

VI. REVISION DATE

14/03/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From NL/H/2565/001/DC to IE/H/1156/001/DC			