COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Quetiapine Fairmed Healthcare 50 mg, 150 mg, 200 mg, 300 mg and 400 mg, prolonged-release tablets
(quetiapine fumarate)

NL/H/5241/001-005/DC

Date: 3 December 2021

This module reflects the scientific discussion for the approval of Quetiapine Fairmed Healthcare 50 mg, 150 mg, 200 mg, 300 mg and 400 mg, prolonged-release tablets. The procedure was finalised at 6 October 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Quetiapine Fairmed Healthcare 50 mg, 150 mg, 200 mg, 300 mg and 400 mg, prolonged-release tablets, from Fairmed Healthcare GmbH.

The products are indicated for:

- Treatment of schizophrenia.

- Treatment of bipolar disorder:
- For the treatment of moderate to severe manic episodes in bipolar disorder
- For the treatment of major depressive episodes in bipolar disorder
- For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously 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 Fairmed Healthcare.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Seroquel 50 mg, 150 mg, 200 mg, 300 mg and 400 mg film-coated tablets which has been registered in the European Economic Area (EEA) by AstraZeneca UK Ltd. since June 2000.

The concerned member states (CMS) involved in this procedure were Austria and Germany.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Quetiapine Fairmed Healthcare 50 mg tablets are peach coloured, round shaped, biconvex film coated tablets, debossed with 'Q50' on one side and plain on the other and contains as active substance 50 mg of quetiapine (as quetiapine fumarate).

Quetiapine Fairmed Healthcare 150 mg are white to off white, capsule shaped, biconvex, film coated tablets, debossed with 'AB2' on one side and plain on the other and contains as active substance 150 mg of quetiapine (as quetiapine fumarate).

Quetiapine Fairmed Healthcare 200 mg tablets are yellow coloured, round shaped, biconvex film coated tablets, debossed with 'I2' on one side and plain on the other and contains as active substance 200 mg of quetiapine (as quetiapine fumarate).

Quetiapine Fairmed Healthcare 300 mg tablets are light yellow coloured, round shaped, biconvex film coated tablets, debossed with 'Q300' on one side and plain on the other and contains as active substance 300 mg of quetiapine (as quetiapine fumarate).

Quetiapine Fairmed Healthcare 400 mg tablets are white coloured, round shaped, biconvex, film coated tablets debossed with 'I4' on one side and plain on other and contains as active substance 400 mg of quetiapine (as quetiapine fumarate).

The prolonged-release tablets are packed in:

- 50 mg, 150 mg strengths: aluminium-aluminium blisters
- 50 mg, 150 mg, 200 mg, 300 mg, 400 mg strengths: white opaque PVC/PVdC-aluminium blisters
- 150 mg strength: HDPE container with PP child resistant closure

The excipients are:

Tablet core

- 50 mg and 150 mg strengths: lactose monohydrate, hypromellose (K4M and K100 Premium LV CR), sodium chloride, povidone K-30, silicified microcrystalline cellulose (cellulose microcrystalline and silica colloidal anhydrous) (only 50 mg strength), microcrystalline cellulose (PH102) (only 150 mg strength), talc and magnesium stearate (E470b)
- 200 mg, 300 mg and 400 mg strengths: lactose monohydrate, hypromellose (K4M), sodium chloride, povidone K-30, talc and magnesium stearate (E470b)

Film coating

- 50 mg strength: Opadry II 85F540003 Pink (contains poly (Vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), iron oxide red (E172) and iron oxide yellow (E172)).

- 150 mg: Opadry II 85F18422 White (contains poly (Vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 3350 (E1521) an talc (E553b)).

- 200 mg strength: Opadry 03B52117 yellow (contains hypromellose 6 cP (E464), titanium dioxide (E171), macrogol 400 (E1521) and iron oxide yellow (E172)).

- 300 mg strength: Opadry 03B82929 yellow (contains hypromellose 6 cP (E464), titanium dioxide (E171), macrogol 400 (E1521) and iron oxide yellow (E172)).

- 400 mg strength: Opadry 03B58900 white (contains hypromellose 6 cP (E464), titanium dioxide (E171) and macrogol 400 (E1521)).

The five tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is quetiapine fumarate, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is a crystalline powder and is slightly soluble in water. Different polymorphic forms of the drug substance exist and Form-I is used in the drug product.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is in line with the Ph. Eur. and CEP, with additional tests for particle size, polymorphic form and microbiological examination. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for two full-scaled batches of each supplier.

Stability of drug substance
The active substance from both suppliers is stable for five years when stored double polyethylene bags in a polyethylene containers. This aspect has been evaluated within the scope of the CEP procedure by the EDQM and the conclusion is taken from the CEP.

II.3 Medicinal Products

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions are explained. The reference products are analysed and the formulation is

optimised. No *in vitro* effects of alcohol on dissolution have been observed. The discriminatory power of the dissolution method has been demonstrated.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The drug products are manufactured by wet granulation. Process validation data on the product have been presented for three full-scaled batches per strength and batch size in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph. Eur., USP/NF or in-house requirements. These specifications are acceptable.

Microbiological attributes

The microbial quality of finished product will be controlled according to the acceptance criteria of microbiological quality for non-sterile dosage forms given in Ph.Eur chapter <5.1.4> by using the methods given in Ph.Eur chapters <2.6.12> and <2.6.13>. The frequency of microbial quality testing is specified in the drug products specification.

Quality control of drug products

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, average weight of tablets, identification (UV, HPLC), loss on drying, dissolution, related substances, uniformity of dosage units, assay, residual solvents and microbiological examination. The release and shelf-life limits are identical in all cases, except for loss on drying. The acceptance criteria for dissolution at 2, 8 and 24 hours are based on the dissolution profiles of the batches used in the bioequivalence studies and are acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data on three batches per strength and batch size from the proposed production sites have been provided, demonstrating compliance with the specification. A risk evaluation concerning the presence of nitrosamine impurities has been provided and is acceptable.

Stability of drug product

Stability data on the product have been provided on three commercial-scale batches per strength stored at 25 °C/60% RH (six months) and 40 °C/75% RH (18 months for the 150 mg strength, 36 months for the other strengths) in accordance with ICH stability guideline. The batches were stored in the container closure systems intended for marketing: white opaque PVC/PVdC-Alu blisters (all strengths), alu-alu blisters (50 mg and 150 mg) and HDPE containers with 60 or 100 tablets (150 mg strength only). For the drug products of the 50 mg (both container closure systems), 200 mg, 300 mg and 400 mg strengths, a shelf-life of 3 years is proposed, and a shelf-life of 30 months for the 150 mg drug products (all container

closure systems). These shelf-lives are acceptable. These medicinal products do not require any special storage conditions. Photostability studies were performed in accordance with ICH recommendations and showed that the products arestable when exposed to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate has been obtained from milk and a declaration is provided that no BSE/TSE risks are present. There are no other substances of ruminant or animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Quetiapine Fairmed Healthcare have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Quetiapine Fairmed Healthcare are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

These products are generic formulations of Seroquel which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Quetiapine fumarate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted ten bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profiles of the test products Quetiapine Fairmed Healthcare 50 mg, 150 mg, 200 mg and 400 mg, prolonged-release tablets (Fairmed Healthcare GmbH, Germany) are compared with the pharmacokinetic profiles of the reference products Seroquel XL, 50 mg, 150 mg (AstraZeneca UK Ltd., Belgium) 200 mg and 400 mg film-coated tablets (AstraZeneca UK Ltd., The Netherlands). The clinical studies for the 50 mg and 150 mg will be discussed separately from the clinical studies for the 200 mg and 400 mg product strengths.

The choice of the reference products in the bioequivalence studies has been justified by a comparison of dissolution results and compositions between the drug products and reference products. The formula and preparation of the bioequivalence batches are identical to the formula proposed for marketing.

<u>Bioequivalence studies with the 50 mg product</u>
To support the application for the 50 mg, the MAH has submitted three bioequivalence studies, namely a study under fasting and fed conditions, and a steady-state study. Since Quetiapine Fairmed Healthcare are prolonged-release tablets, submission of these types of bioequivalence studies was considered adequate. The choice of the reference product in the bioequivalence studies has been justified by a comparison of dissolution results and compositions between the drug product and reference product.

Study I – Fasted state study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy, non-smoking, adult, human subjects, aged 18-55 years. Each subject received a single dose (50 mg) of one of the two quetiapine fumarate formulations. The tablet was orally administered with 240 ml water after at least ten hours of fasting. There were two dosing periods, separated by a washout period of seven 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, 12, 14, 16, 20, 24 and 36 hours after administration of the products.

The design of the study is acceptable.

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 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. 54 subjects were eligible for pharmacokinetic analysis.

Table 1. 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)	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
CV coefficient of variation

**ln-transformed values*

Study II – Fed state study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 80 healthy, non-smoking, adult, human subjects, aged 18-55 years. After an overnight fast of at least ten hours, subjects were served a standardized high fat high calorie vegetarian breakfast, which they consumed within 30 minutes. Each subject received a single dose (50 mg) of one of the two quetiapine fumarate formulations 30 minutes after serving of high fat high calorie vegetarian breakfast. The nutritional composition of the meal was as follows: 137 kcal protein, 540 kcal of fat and 260 kcal of carbohydrates. The total energy content of the meal was 938 kcal. The

tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of seven days.

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

The design of the study is acceptable.

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 five subjects were withdrawn from the study. 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 personal reasons. 75 subjects were eligible for pharmacokinetic analysis.

Table 2. 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	1102 ± 473	132 ± 61	5.55 (4 – 12)	1295 ± 630
Reference	1330 ± 663	1156 ± 470	142 ± 64	6 (3 – 12)	1330 ± 663
***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
CV coefficient of variation

**ln-transformed values*

Study III – Steady state study

Design

A multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under steady-state conditions in 58 (including two additional subjects) healthy, non-smoking, adult, human subjects, aged 18-55 years. Each subject received four doses (50 mg) of one of the two quetiapine fumarate formulations. The tablet was orally administered with 240 ml water after at least ten hours of fasting. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected at 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, 14, 16, 20, 24 and 36 hours after administration of the products in each period.

The design of the study is acceptable.

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 their own accord. They were replaced with the two additional subjects. 56 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=56	**AUC_{0-t}** (ng.h/ml)	**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_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index

**ln-transformed values*

Conclusion on bioequivalence studies for the 50 mg tablets

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Achievement of steady-state appeared to be reached in the steady-state study. Based on the submitted bioequivalence studies Quetiapine Fairmed Healthcare 50 mg is considered bioequivalent with Seroquel 50 mg, under fasting and fed conditions, and in the steady-state.

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).

Bioequivalence studies with the 150 mg product

To support the application for the 150 mg product, the MAH has submitted three bioequivalence studies, namely a study under fasting and fed conditions, and a steady-state study. Since Quetiapine Fairmed Healthcare are prolonged-release tablets, submission of these types of bioequivalence studies was considered adequate. The choice of the reference product in the bioequivalence studies has been justified by a comparison of dissolution results and compositions between the drug product and reference product

Study IV – Fasted state study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 72 healthy, non-smoking, adult, human subjects, aged 18-45 years. Each subject received a single dose (150 mg) of one of the two quetiapine fumarate formulations. The tablet was orally administered with 240 ml water after at least ten hours of fasting. There were two dosing periods, separated by a washout period of eight 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, 12, 14, 16, 20, 24, 36 and 48 hours after administration of the products in each period.

The design of the study is acceptable.

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 were withdrawn from the study on medical grounds in Period-I and two subjects discontinued from the study on their own accord in Period-II. 68 subjects were eligible for pharmacokinetic analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of quetiapine fumarate under fasted conditions.

Treatment N=68	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	4014.5 ± 1520.6	4135.1 ± 1630.6	235.0 ± 98.1	12.0 (2.0 – 4.0)
Reference	4125.8 ± 1551.2	4210.7 ± 1617.6	244.1 ± 78.4	12.0 (3.0 – 24.0)
***Ratio (90% CI)**	0.97 (0.90 – 1.04)	0.98 (0.91 – 1.04)	0.94 (0.88 – 1.01)	-
CV (%)	24.1	23.9	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
CV coefficient of variation

**ln-transformed values*

Study V – Fed state study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 72 healthy, non-smoking, adult, human subjects, aged 18-45 years. After an overnight fast of at least 10 hours, subjects were served a standardized high fat high calorie vegetarian breakfast, which they consumed within 30 minutes. Each subject received a single dose (150 mg) of one of the two quetiapine fumarate formulations 30 minutes after serving of high fat high calorie vegetarian breakfast. The nutritional composition of the meal was as follows: 137 kcal protein, 260 kcal of fat and 540 kcal of carbohydrates. The total energy content of the meal was 938 kcal. The tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of eight days.

Blood samples were collected at 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, 14, 16, 20, 24, 36 and 48 hours after administration of the products in each period.

The design of the study is acceptable.

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 seven subjects were withdrawn from the study. One subject was withdrawn from the study on medical grounds in Period-I. Four subjects were withdrawn from the study on medical grounds in Period-II. One subject discontinued from the study on his own accord in Period-II and one subject was withdrawn from the study on the grounds of protocol noncompliance in Period-II. 65 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=65	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	2979.5 ± 1342.7	3009.1 ± 1351.6	308.5 ± 127.1	5.5 (3.5 – 12.0)
Reference	2881.5 ± 1217.8	2908.8 ± 1234.1	329.2 ± 140.9	5.5 (3.0 – 12.0)
***Ratio (90% CI)**	1.03 (0.97 – 1.08)	1.03 (0.98 – 1.08)	0.93 (0.87 – 1.00)	-
CV (%)	18.2	18.3	25.1	-

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Study VI – Steady state study

Design

A multiple-dose, randomised, two-way crossover bioequivalence study was carried out under fasted conditions in 84 healthy, non-smoking, adult, human subjects. Each subject received a single dose (150 mg) of one of the two quetiapine fumarate formulations. The tablets were orally administered with 240 ml water after at least ten hours of fasting. No food was allowed for at least 5 hours post-dose.

Blood samples were collected as follows:

- Days 1, 5, 6, 10 and 11: pre-dose
- Days 7 and 12: 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, 14, 16, 20 and 24 hours post-dose.

The design of the study is acceptable.

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

Group I: in total three subjects were withdrawn from the study. One subject withdrew from the study due to his personal reason prior to dosing on Day 08. One subject withdrew from the study prior to dosing on Day 03 and one subject was dismissed from the study due to abnormal ECG prior to dosing on Day 11. 39 subjects were eligible for pharmacokinetic analysis.

Group II: in total one subject was dismissed from the study due to abnormal ECG prior to dosing on Day 04. 41 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=80	**AUC_{0-t} (ng.h/ml)**	**$C_{t,ss}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	2024.9 ± 830.8	41.6 ± 26.7	157.2 ± 65.4	5.5 (1.0 – 16.0)
Reference	2058.0 ± 852.5	35.4 ± 19.3	179.2 ± 76.6	5.5 (2.0 – 16.0)
***Ratio (90% CI)**	0.98 (0.94 – 1.02)	0.88 (0.83 – 0.93)	1.11 (1.00 – 1.23)	-
CV (%)	15.8	22.5	41.2	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
$C_{t,ss}$ plasma concentration at steady state
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies for the 150 mg tablets

The 90% confidence intervals calculated for AUC_{0-t}, $C_{t,ss}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25, in both fasting and fed conditions and in steady-state). Based on the submitted bioequivalence studies Quetiapine Fairmed Healthcare 150 mg is considered bioequivalent with Seroquel 150 mg.

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).

Bioequivalence studies with the 200 mg and 400 mg products

To support the application for 200, 300 and 400 mg prolonged-release tablets, the MAH has submitted four bioequivalence studies, namely a study under fasting conditions, under non-high fat diet, under high fat diet and a steady-state study.

Study VII – Fasted state study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover 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 two quetiapine fumarate formulations. The tablet was orally administered with 240 ml water after at least ten hours of fasting. There were two dosing periods, separated by a washout period of seven 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 product.

The design of the study is acceptable.

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 nine subjects were withdrawn from the study. One subject withdraw his informed consent, two subjects were withdrawn due to protocol violation (positive alcohol breath test) and six due to adverse events or on medical grounds. 71 subjects were eligible for pharmacokinetic analysis.

Table 7. 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
CV coefficient of variation

**ln-transformed values*

Study VIII – Fed state study (non-high fat diet)

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 66 healthy male subjects, with mean age 27.3 years. After a fast of at least 10 hours, subjects were served a non-high fat breakfast, which they consumed within 30 minutes. 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. Each subject received a single dose (200 mg) of one of the two quetiapine fumarate formulations 30 minutes after serving of a non-high fat high calorie vegetarian breakfast. The tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected at 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 in each period.

The design of the study is acceptable.

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. Three subjects withdrew their informed consent and nine were withdrawn due to adverse events or on medical grounds. 52 subjects were eligible for pharmacokinetic analysis.

Table 8. 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	4066 ± 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)**	1.03 (1.00 – 1.05)	1.02 (0.99 – 1.05)	1.15 (1.09 – 1.21)	-	-
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
CV coefficient of variation

**ln-transformed values*

Study IX – Fed state study (high fat diet)

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 64 healthy Asian male subjects, aged 22-44 years. After a fast of at least 10 hours, subjects were served a high fat breakfast, which they consumed within 30 minutes. The nutritional composition of the meal was as follows: 137 kcal protein, 260 kcal of fat and 540 kcal of carbohydrates. Each subject received a single dose (200 mg) of one of the two quetiapine fumarate formulations 30 minutes after serving of a non-high fat high calorie vegetarian breakfast. The tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of 17 days.

Blood samples were collected at 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 in each period.

The design of the study is acceptable.

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 subject was withdrawn on the day of dosing in Period II due to emesis. 63 subjects were eligible for pharmacokinetic analysis.

Table 9. 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 ± 1.1
Reference	4185 ± 2152	4220 ± 2157	398 ± 168	5.5 (3 – 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
CV coefficient of variation

**ln-transformed values*

Study X – Steady state study
Design
A multiple-dose, randomised, two-treatment, two-period, two-sequence, crossover bioequivalence study was carried out under steady state conditions in 100 patients with schizophrenia, with a mean age of 32.8 years. Single oral doses (400 mg) of one of the two quetiapine fumarate formulations were administered together with 150 mL of water on study days one to eight. Cross-over took place at day five. The patients had fasted for at least eight hours prior to drug administration.

The venous blood samples were collected 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 consider as pre-dose sample for Dose-05). The design of the study is acceptable.

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. 98 subjects were eligible for pharmacokinetic analysis.

Table 10. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of quetiapine fumarate under fasted conditions.

Treatment N=98	AUC_{0-t} (ng.h/ml)	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_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index

**ln-transformed values*

Conclusion on bioequivalence studies for the 200 mg and 400 mg tablets

For the 200 mg formulation (fasting and fed state) and 400 mg formulation (steady state) the mean ratios of all the primary pharmacokinetic parameters between the test products and reference products are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Quetiapine Fairmed Healthcare 200 mg and 400 mgare considered bioequivalent with the respective Seroquel product strengths.

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).

Biowaiver

The MAH requested a biowaiver for the 300 mg product strength. To support this biowaiver, the MAH has performed four bioequivalence studies with two different strengths: a study in fasted conditions with the 200 mg strength, two studies in the fed state with the 200 mg strength and a steady state study with the 400 mg strength. The recommendation for single-unit prolonged release formulations is that a single dose study in fasting state is performed with each strength. However with quetiapine, for safety reasons it may be acceptable to extrapolate the results of a bioequivalent study with a single strength to other strengths, if the criteria for a biowaiver between strengths are fulfilled. Also, the steady-state study in patients with the highest dose provides reassurance that extrapolation to 300 mg is possible.

The following criteria for a biowaiver, in accordance with the *Guideline on the Investigation of Bioequivalence*, have been met:

1. The drug products (Quetiapine 200, 300 and 400 mg prolonged-release tablets)] are manufactured at the same manufacturing site using a similar manufacturing process.
2. The kinetics of quetiapine fumarate are linear over the therapeutic range.
3. All the strengths (200 mg, 300 mg and 400 mg) have same qualitative composition except coloring/film coating agent.
4. The compositions of the 200 mg, 300 mg and 400 mg strengths are quantitatively proportional, i.e. the ratio between the amounts of each excipient to the amount of active substance is the same for all three strengths.
5. Appropriate *in vitro* dissolution results suffice the requirements for biowaiver.

Similarity in dissolution profiles has been shown at all pH conditions between the additional 300 mg strength, the 200 mg biobatch and the 300 mg biobatch. Similarity in dissolution has not been shown between the two biobatches, the 200 and 400 mg strength, at pH 4.5 and 6.8. However, since bioequivalence has been shown between the test and the reference product for the 200 and 400 mg strength, the *in vivo* results prevail. All other conditions for the biowaiver are met. Therefore, a biowaiver for the 300 mg strength has been granted.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Quetiapine Fairmed Healthcare.

Table 11. Summary table of safety concerns as approved in RMP

Important identified risks	Nervous system disorders: - Extrapyramidal symptoms (EPS) - Somnolence Metabolism and nutritional disorders: - Weight gain - Lipid changes - Hyperglycaemia and diabetes mellitus - Metabolic risk factors Psychiatric disorders: - Suicide and suicidality
Important potential risks	Nervous system disorders: - Cerebrovascular adverse events in elderly - Cerebrovascular adverse events in non-elderly patients

	Cardiac disorders: - Torsade de Pointes - Ischaemic heart disease Injury, poisoning, procedural complications: - Abuse and misuse
Missing information	- Use in pregnant or breast feeding women - Use in patients on concomitant cardiovascular medications - Use in patients on concomitant valproic acid

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

Risk minimisation measures

In line with the innovator medicinal product the MAH states that additional Risk Minimisation measures are in place for the following safety concerns: Nervous system disorders: Extrapyramidal symptoms (EPS), Somnolence; Metabolism and nutritional disorders: Weight gain, Lipid changes, Hyperglycaemia and diabetes mellitus and Metabolic risk factors. Details of the key elements for additional Risk minimisation measures are provided in Annex 6 of the RMP, this is acceptable. The objectives, rationale, target audience and 'plans to evaluate the effectiveness of the interventions and criteria for success' proposed by the MAH are agreed.

In part V.2. Additional Risk Minimisation Measures the MAH should amend the proposed distribution of the aRMM. The exact content and distribution of aRMM are agreed upon by the National Competent Authority of member states.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Seroquel. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the products is similar to the pharmacokinetic profile of the reference products. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

The package leaflet (PL) 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 language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Quetiapine Fairmed Healthcare 50 mg, 150 mg, 200 mg, 300 mg and 400 mg, prolonged-release tablets have a proven chemical-pharmaceutical quality and are generic forms of Seroquel film-coated tablets. Seroquel are well-known medicinal products with established favourable efficacy and safety profiles. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Fairmed Healthcare with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 October 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse