CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Quetiafair 25 mg, 100 mg, 200 mg and 300 mg, film-coated tablets Quetiafair 4-Day Starterpack Fair-Med Healthcare GmbH, Germany

quetiapine fumarate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2300/001-005/DC
Registration number in the Netherlands: RVG 109302, 109304, 109306-109308

24 September 2012

Pharmacotherapeutic group:	antipsychotics; diazepines, oxazepines and thiazepines
ATC code:	N05AH04
Route of administration:	oral
Therapeutic indication:	schizophrenia and prevention of relapse in stable schizophrenic patients; moderate to severe manic episodes; major depressive episodes
Prescription status:	prescription only
Date of authorisation in NL:	6 September 2012
Concerned Member States:	Decentralised procedure with IT
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 Quetiafair 25 mg, 100 mg, 200 mg and 300 mg, film-coated tablets and Quetiafair 4-Day Starterpack from Fair-Med Healthcare GmbH. The date of authorisation was on 6 September 2012 in the Netherlands.

The product is indicated for treatment of:

- schizophrenia.
- 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.

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

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1- and D_2- receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine. Additionally, N-desalkyl quetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic a_1 receptors, with a lower affinity at adrenergic a_2 and serotonin $5HT_1A$ receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Seroquel 25 mg, 100 mg, 200 mg and 300 mg film-coated tablets which have been registered in the UK by Astra-Zeneca UK Ltd since 31 July 1997 (original product). The Dutch reference medicinal products are Seroquel® 25 mg, 100 mg, 200 mg and 300 mg film-coated tablets (NL license RVG 20826-20827, 20828 and 25603), and Seroquel® - 4-Day Starterpack (NL license RVG 25128). 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 submitted a bioequivalence study in which the pharmacokinetic profile of the 25 mg product is compared with the pharmacokinetic profile of the reference product Seroquel 25 mg film-coated tablets from the UK market. 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. These generic products can be used instead of their reference products.

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 medicinal product.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is quetiapine fumarate, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.*) or any other pharmacopoeia. It is a white to off white powder, which is soluble in dimethylsulphoxide and insoluble in water. The polymorphic form produces 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 six 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 drug substance specification has been established with in-house and Ph.Eur. methods. The specifications are acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale production batches

Stability of drug substance
Stability data on the active substance have been provided for three production-scale, three pilot-scale, and three R&D batches. They were stored at 25°C/60% RH (resp. 9 months, 36 months, and 36 months) and at 40°C/75% RH (6 months for all batches). Results of the accelerated and long-term storage conditions showed no specific up or downward trends in any of the parameters tested. The claimed re-test period of 4 years without special storage conditions 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
Quetiafair 25 mg is a peach, round, biconvex film coated tablet with a diameter of approximately 5.7mm.
Quetiafair 100 mg is a yellow, round, biconvex film coated tablet with a score line on one side and a diameter of approximately 9.1mm.
Quetiafair 200 mg is a white, round, biconvex film coated tablet with a score line on one side and a diameter of approximately 12.1mm.
Quetiafair 300 mg is a white, oblong, biconvex film coated tablet with a score line on one side. The tablet is approximately 7mm thick, 19mm long & 9mm wide.

The Starterpack contains 6 tablets of quetiapine (as quetiapine fumarate) of 25 mg, 3 tablets of 100 mg and 1 tablet of 200 mg

The 100, 200 and 300 mg tablets can be divided into equal halves.

The film-coated tablets are packed in opaque PVC/aluminium blisters.

The excipients are:
Tablet core
Hypromellose (E464)
Calcium hydrogen phosphate dihydrate
Lactose monohydrate
Maize starch
Sodium starch glycolate Type A
Magnesium stearate (E572)
Microcrystalline Cellulose pH 102 (E460)
Talc (E553b)
Silica colloidal anhydrous

Film-coating
25 mg:
Iron oxide red and yellow (E 172)
Hypromellose 2910 (E464)
Titanium dioxide (E171)
Macrogol 400
Sunset yellow FCF Aluminium lake (E110)

100 mg:
Iron oxide yellow (E 172)
Hypromellose 2910 (E464)
Titanium dioxide (E171)
Macrogol 400

200 & 300 mg:
Hydroxypropyl cellulose (E463)
Hypromellose 2910 (E464)
Talc (E553b)
Titanium dioxide (E171)

The different strengths are fully dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to create a film-coated tablet which could be considered bioequivalent to innovator product Seroquel®. The choices of the packaging and manufacturing process are justified. Comparative dissolution profiles have been submitted for:

- The products used in the bioequivalence study;
- The products used in the bioequivalence study and the Dutch innovator product (Seroquel/NL 25 mg tablets);
- All strengths of the product for registration;
- Comparative dissolution profiles of the biobatch versus the innovator products marketed in all the CMSs involved in the DCP procedure.

All tablets tested showed comparative dissolution behaviour (more than 80% dissolved after 15 minutes).
The pharmaceutical development has been sufficiently explained.

Manufacturing process

The tablets are manufactured by means of a process including wet granulation, drying, mixing, compression, coating and packing. The manufacturing process has been adequately validated according to relevant European guidelines.
Process validation data on the product has been presented four production-scale batches of the common blend and three pilot-scale batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorization.

Control of excipients
All excipients comply with the specifications of the Ph.Eur except for the Opadry® coating material. For the Opadry coating material an internal specifications is given. The substances used in the Opadry coating are listed in the Ph.Eur., except for iron oxide and sunset yellow, which are in conformity with Directive 95/45/EC and 78/25/EEC. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, uniformity of dosage units (mass variation), uniformity of mass of the subdivided parts (300 mg tablet), loss on drying, hardness, identification by HPLC, identification of the colorants, assay, disintegration, dissolution, related substances, and microbiological contamination. The breakability of the 100, 200 and 300 mg tablets is included in the specification and is according to the Ph.Eur. Release and end of shelf-life specification are identical except for the average weight and loss on drying. The limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches of each strength demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three pilot-scale batches of the 25 mg, 100 mg, 200 mg and 300 mg product stored at 25°C/60%RH (36 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 in PVC/Aluminum blisters. Results stayed within limits although a slight increase of the water content under all conditions was seen. Photostability testing showed that the drug product was stable under light. A shelf-life of 36 months was granted for all strengths, without further storage conditions

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient of animal origin. A statement of the manufacturer of lactose monohydrate regarding the safety and compliance to Ph.Eur. current edition, a statement from the Opadry manufacturer regarding the material origin as well as a statement for the vegetable origin of magnesium stearate have been presented.

II.2 Non-clinical aspects

These products are generic formulations of Seroquel 25 mg, 100 mg, 200 mg and 300 mg tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
A short statement on the environmental risk has been provided, stating no environmental risk assessment is required, since the present product is a generic equivalent of the innovator and it is only going to substitute a percentage of the total prescriptions of the innovator. It is therefore not going to increase the amounts of quetiapine fumarate that is released into the environment. This is deemed acceptable.

II.3 Clinical aspects

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Quetiafair 25 mg (Fair-Med Healthcare GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Seroquel 25 mg tablets (AstraZeneca, UK).
The study is performed with the lowest strength of 25 mg, for reasons of intolerance. This is in line with the recommended posology of a low starting dose and gradual up-titration.

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 in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 38 healthy subjects (19 males, 19 females), aged 18-54 years. Each subject received a single dose (25 mg) of one of the 2 quetiapine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. With the exception of the volume administered at the time of dosing, fluids were not permitted from 2 hours before dosing to 2 hours after dosing, but water was permitted *ad libitum* at all other times. There were 2 dosing periods, separated by a washout period of 9 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 7, 8, 10, 12, 16, and 24 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate, half-lives and the dosage used in the bioequivalence study. Also the washout period is acceptable.

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

Results
One subject withdrew for personal reasons. Thirty-seven subjects were eligible for pharmacokinetic analysis.

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

Treatment N=37	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	277 ± 169	285 ± 175	80.5 ± 46.5	0.75	4.6 ± 1.1
Reference	261 ± 133	269 ± 140	73.3 ± 34.2	1.0	4.7 ± 1.2
***Ratio (90% CI)**	1.03 (0.95 – 1.13)	1.04 (0.95 – 1.12)	1.03 (0.94 – 1.14)	--	--
CV (%)	21	21	25	--	--

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of quetiapine under fasted conditions, it can be concluded that Quetiafair 25 mg and Seroquel 25 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Quetiapine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of quetiapine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to other strengths
The results of the bioequivalence study performed with the 25 mg tablet apply to the other strengths. The products fulfil the conditions of the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98.*

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

Risk management plan
Quetiapine was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of quetiapine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. However, it is noted that for the innovator product an RMP has been constituted. The RMP of the innovator should be followed, where appropriate.

The following issues should be 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.

The SPC for the product should follow and be kept in line with that of the innovator.

The MAH should follow, where appropriate, the risk minimisation activities of the innovator, e.g. participate in DHPCs where needed, produce and distribute educational material for patients and physicians when applicable, etc. In line with the reference product, this means that awareness of appropriate metabolic monitoring should be promoted of the published utilised guidelines regarding metabolic monitoring when atypical antipsychotics are used.

Product information

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

Readability test

The package leaflet has not been evaluated via a user consultation study. Reference is made to the successfully user tested PL for another procedure, concerning Quetiapine 25 mg, 100 mg, 150 mg, 200 mg & 300 mg film-coated tablets. The bridging report is considered acceptable and is approved.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Quetiafair 25 mg, 100 mg, 200 mg and 300 mg, film-coated tablets and Quetiafair 4-Day Starterpack have a proven chemical-pharmaceutical quality and are generic forms of Seroquel® 25 mg, 100 mg, 200 mg and 300 mg film-coated tablets, and Seroquel® - 4-Day Starterpack. 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.

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 Quetiafair 25 mg, 100 mg, 200 mg and 300 mg, film-coated tablets and Quetiafair 4-Day Starterpack with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 16 March 2012. Quetiafair 25 mg, 100 mg, 200 mg and 300 mg, film-coated tablets and Quetiafair 4-Day Starterpack were authorised in the Netherlands on 6 September 2012.

The date for the first renewal will be: 16 March 2017.

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

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached