CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Quetiapine Jubilant 25 mg, 100 mg, 150 mg, 200 mg and 300 mg, film-coated tablets Jubilant Pharmaceuticals N.V., the Netherlands

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 104297-104301

30 January 2013

Pharmacotherapeutic group:	antipsychotics; diazepines, oxazepines and thiazepines
ATC code:	N05AH04
Route of administration:	oral
Therapeutic indication:	schizophrenia; moderate to severe manic episodes in bipolar disorder; major depressive episodes in bipolar disorder; prevention of recurrence in patients with bipolar disorder
Prescription status:	prescription only
Date of authorisation in NL:	14 September 2011
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 Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Quetiapine Jubilant 25 mg, 100 mg, 150 mg, 200 mg and 300 mg, film-coated tablets from Jubilant Pharmaceuticals N.V. The date of authorisation was on 14 September 2011 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 national procedure concerns a generic application claiming essential similarity with the innovator products Seroquel® 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated tablets (NL license RVG 20826-20827, 25602, 20828 and 25603), which have been registered in the Netherlands by AstraZeneca B.V. since 1998 (25, 100 & 200 mg) and 2001 (150 & 300 mg).

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 product is compared with the pharmacokinetic profile of the reference product Seroquel 25 mg film-coated tablets, obtained from the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

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

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic 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. The active substance is an off white to creamy powder, which is soluble in dimethylsuphoxide and dimethyl formamide and exhibits polymorphism. Comparison with that of innovator's tablet Seroquel, confirms the same single morphology (Form I). Quetiapine fumarate does not exhibit stereochemistry or isomerism.

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
Quetiapine fumarate is synthesised in 5 steps. Sufficient information was provided regarding starting materials, solvents and reagents. The active substance has been adequately characterized.

Quality control of drug substance
The drug substance specification has been established in-house. The set specifications for the solvents currently included are in accordance with the NfG on Impurities: residual solvents are therefore acceptable. The limits set for related substances are in accordance with the NfG on impurities testing: 'impurities in new drug substances' and are thus deemed acceptable.
Batch analytical data demonstrating compliance with the drug substance specification have been provided on 3 batches.

Stability of drug substance
Stability data on the active substance have been provided for three production-scale batches stored at 25°C/60% RH for 36 months and 40°C/75% RH for six months. No significant changes were observed at any of the storage conditions. A re-test period of 36 months is considered acceptable.

** 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 Jubilant 25 mg are peach coloured, round, biconvex, film coated tablets, debossed with "J" on one side and "25" on the other side.
Quetiapine Jubilant 100 mg are yellow coloured, round, biconvex, film coated tablets, debossed with "J" on one side and "100" on the other side.
Quetiapine Jubilant 150 mg are yellow coloured, round, biconvex, film coated tablets, debossed with "J" on one side and "150" on the other side.

Quetiapine Jubilant 200 mg are white, round, biconvex, film coated tablets, debossed with “J” on one side and “200” on the other side.
Quetiapine Jubilant 300 mg are white, capsule shaped, film coated tablets, debossed with “J” on one side and “300” on the other side.

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

The excipients are:
Tablet core - lactose monohydrate, dibasic calcium phosphate dehydrate, microcrystalline cellulose, sodium starch glycolate, povidone K-90, magnesium stearate,
Coating - hypromellose 5, titanium dioxide, macrogol 400, yellow iron oxide (25 mg/100 mg/150 mg) and red iron oxide (25 mg).

All tablet 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 also confirmed that the proposed excipients are very similar to those of the reference drug Seroquel. The batches used in the bioequivalence study were considered comparable with respect to impurities, appearance, assay and uniformity of dosage units.
Comparative dissolution studies of the 25 mg strength of quetiapine film-coated tablets against all the other strengths were respectively performed in pH 1.2, pH 4.5 and pH 6.8. Data have also been provided for the products (all strengths) at issue and their corresponding strength of the reference product. The results are comparable. Use of the UK reference product is acceptable, based on comparable dissolution profiles of each strength of the UK product versus the same strength of the Dutch product.

Manufacturing process
The tablets are manufactured by wet granulation, compression of the lubricated granules into tablets and subsequent coating and drying. The manufacturing process has been adequately validated according to relevant European guidelines. Validation is supported by batch analysis results of two pilot-scale batches of each of the five strengths. All batches comply with the proposed set of specifications. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
Except for the colourants, all excipients comply with the European Pharmacopoeia. In-house test and control procedures are followed for the colourants. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity of active substance and colourants, assay, related substances, water, dissolution, disintegration, Uniformity of dosage form and microbial purity. The release and shelf-life requirements/limits are identical. The other specifications and limits are common and acceptable for immediate release tablets. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site at have been provided on two pilot-scale batches for all five strengths, demonstrating compliance with the release specification. Batch analytical data of commercial batches will be provided when available.

Stability of drug product
Stability data on the product has been provided on two pilot-scale batches stored at 25ºC/60% RH and 40ºC/60% RH for 18 months and 6 months respectively. The batches were stored in the proposed marketing containers, i.e. aluminium blister packs and also in simulated bulk packs for 6 months at 25ºC/60% RH.
The conditions used in the stability studies are according to the ICH stability guideline. In photostability studies no significant degradation occurred.

No significant changes were observed for any of the packaging at any of the storage conditions and therefore, a shelf-life of 24 months without any special storage condition is acceptable. Post approval the shelf life has been extended to 36 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate and magnesium stearate are of animal origin. TSE/BSE declarations have been provided by the respective suppliers, confirming compliance with the NfG on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Products.

II.2 Non-clinical aspects

This product is a generic formulation of Seroquel which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board 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 released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Quetiapine is a well-known active substance with established efficacy and tolerability. 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 Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Quetiapine Jubilant 25 mg (Jubilant Pharmaceuticals N.V., NL) is compared with the pharmacokinetic profile of the reference product Seroquel 25 mg film-coated tablets (AstraZeneca UK Limited, 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.
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 36 healthy male subjects. Each subject received a single dose (25 mg) of one of the 2 quetiapine formulations. The tablet was orally administered with 240 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00 and 36.00 hours after administration of the products.

The design of the study, including the use of the lowest dose, and sampling schedule are 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 from the study due to an adverse event (giddiness associated with drowsiness). Another subject did not report to the facility for admission in Period II. The remaining 34 subjects were included in the analysis.

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

Treatment N=34	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	524.06 ± 202.24	543.22 ± 212.37	164.17 ± 75.20	0.9	0.5-2.5
Reference	507.61 ± 181.44	523.58 ± 186.81	160.96 ± 64.41	0.9	0.5-2.5
***Ratio (90% CI)**	1.02 (0.94-1.11)	1.02 (0.95-1.11)	1.01 (0.91-1.13)	--	--
CV (%)	20.3	20.4	26.9	--	--

$AUC_{0-\infty}$ 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 Quetiapine Jubilant 25 mg and Seroquel 25 mg film-coated 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 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of quetiapine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not

adequately covered by the current SPC. 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:

- Extrapyramidal symptoms (EPS) including tardive dyskinesia (TD), somnolence, syncope and orthostatic hypotension including falls and fractures, seizures, neutropenia, weight gain, increased cholesterol and triglycerides, hyperglycaemia and diabetes mellitus, hypothyroidism, anaphylaxis, jaundice, hepatitis, increased serum transaminases and gamma-GT, Stevens Johnson syndrome (SJS), neuroleptic malignant syndrome (NMS)
- Agranulocytosis, cerebrovascular adverse events (CVAEs) in elderly and in non-elderly, QTc prolongation, Torsade de pointes and interaction with drugs known to cause electrolyte imbalance or to increase QTc interval, sudden death, myocarditis, hyperprolactinaemia and clinical consequences such as galactorrhoea, cataracts, increased mortality in elderly demented patients, suicidality, pancreatitis, off label use including off label paediatric use, dysphagia and related events, SIADH and hyponatraemia, aggression/agitation, rhabdomyolysis and increased CPK, serotonin syndrome (SS),interaction with valproate, interaction with methadone, false positive laboratory results especially for benzodiazepines and methadone, abuse and misuse
- Interaction with cardiovascular drugs, renally impaired patients, pregnant or lactating women, patients of different or selected ethnic origin, elderly

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.

Product information

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

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Both rounds of testing showed that, for each question, 100% of participants were able to find the correct information, and 100% of participants were able to answer the questions correctly. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Quetiapine Jubilant 25 mg, 100 mg, 150 mg, 200 mg and 300 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Seroquel® 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated 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.

The Board followed the advice of the assessors.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Quetiapine Jubilant 25 mg, 100 mg, 150 mg, 200 mg and 300 mg, film-coated tablets were authorised in the Netherlands on 14 September 2011.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to submit batch analytical results of the first three commercial-scale batches of each strength.

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
Request for change in the product information following PhVWP/ CMDh decision; risk of extrapyramidal effects and withdrawal symtoms in newborns after exposure during the third trimester of pregnancy.	--	IB	6-12-2011	18-1-2011	Approval	N
Transfer of the marketing authoristion.	--	IB MA transfer	16-1-2012	3-2-2012	Approval	N
Upadate of the SPC and PL in view of the originator SPC and PL.	--	IB	13-3-2012	23-3-2012	Approval	N
Grouped IB variations regarding quality aspects of the drug substance and drug product, including extension of the shelf life to 36 months.	--	IB/G	16-3-2012	2-5-2012	Approval	N
Addition of a batch control site.	--	IA	8-6-2012	10-8-2012	Approval	N
Introduction or change of the Pharmaeovigilance System Master File (PSMF).	--	IA	21-8-2012	10-9-2012	Approval	N
Change in the name and/or address of a manufacturer of the finished product, including quality control sites.	--	IA	23-11-2012	16-1-2013	Approval	N