LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Quetiapin Orion
(quetiapine fumarate)

SE/H/1762/01-04/DC
2017-1478, 2017-1479, 2017-1480, 2017-1481

This module reflects the scientific discussion for the approval of Quetiapin Orion. The procedure was finalised on 2018-12-20. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

The application for Quetiapin Orion, 25 mg, 100 mg, 200 mg and 300 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI, NO and PL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Seroquel, 25 mg, 100 mg, 200 mg film-coated tablet, authorised in UK since 2000, with AstraZeneca UK Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Seroquel, 200 mg, film-coated tablet, from UK with AstraZeneca UK Limited as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS PL: Seroquel, 25 mg, 100 mg, 200 mg and 300 mg, film-coated tablet authorised in SE since 2003, with AstraZeneca AB as marketing authorisation holder.
The justification to use this product is based on RMS's own files. The ERP information was circulated during validation period.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Quetiapine Fumarate, 200 mg, film-coated tablets with the reference product Seroquel, 200 mg, film-coated tablets.

Pharmacokinetic properties of the active substance

Absorption: Quetiapine is well absorbed and extensively metabolised following oral administration.

The pharmacokinetics of quetiapine is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range.

Elimination: The terminal half-life of quetiapine and norquetiapine is 7 and 12 hours, respectively.

Bioequivalence study

Methods

This was a single-dose, two-way crossover study conducted in 36 healthy volunteers (27 completed), comparing Quetiapine Fumarate, 200 mg, film-coated tablets with Seroquel, 200 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of quetiapine were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 03rd April 2017 and 01st June 2017.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for quetiapine, n=27.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	4474.95 ±1646.11	999.64 ± 259.23	0.75 (0.50-4.00)
Reference	4377.52 ± 1593.09	1017.99 ± 334.75	1.00 (0.50-4.00)
***Ratio (90% CI)**	102.02 (97.66 - 106.58)	98.64 (89.72 - 108.45)	-

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 plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 25 mg, 100 mg and 300 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 25 mg, 100 mg and 300 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of quetiapine is linear across the approved dosing range.

The use of the lower strength 200 mg instead of the highest strength 300 mg in the bioequivalence study is acceptable since there are safety concerns with administration of the highest strength 300 mg to healthy volunteers.

Based on the submitted bioequivalence study, Quetiapine Fumarate, 200 mg, film-coated tablets is considered bioequivalent with Seroquel, 200 mg, film-coated tablets.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan (Version 1.1), 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 Quetiapin Orion.

Please, see the report “Non-clinical and clinical assessment of the response to the questions raised by RMS and CMSs” for assessment of the responses.

Safety specification

Summary of safety concerns	
Important identified risks	• Extrapyramidal symptoms (EPS) • Somnolence • Weight gain • Lipid changes (increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs) • Hyperglycaemia and diabetes mellitus • Metabolic risk factors
Important potential risks	• Cerebrovascular adverse events in elderly • Cerebrovascular adverse events in non-elderly patients • Torsade de pointes • Ischaemic heart disease • Potential for off-label use and misdosing • 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

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and additional risk minimisation activities are proposed by the applicant according to below, which is endorsed.

Educational material for healthcare professionals for following safety concerns: Extrapyramidal symptoms (EPS); Somnolence; Weight gain; Lipid changes (increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs); Hyperglycaemia and diabetes mellitus; Metabolic risk factors; Potential for off-label use and misdosing.
Note! Educational material is not a conditional for marketing authorisation (VII.3).

Objectives:
To provide additional information to prescribing physicians.

Rationale for the additional risk minimisation activity:
To provide specific information for prescribing physicians in regard to these risks. The reference medicinal product has similar additional risk minimisation activity.

Target audience and planned distribution path:
The details of the communication plan will be agreed with each national competent authority prior to the launch of the product. The main target audience of the physician guide include specialists involved with diagnosis and initiation of quetiapine treatment, and physicians involved with follow-up of the treatment. The distribution path will include mailing of the printed material and/or electronic access to the material.

Plans to evaluate the effectiveness of the interventions and criteria for success:
Review in PSURs or other applicable periodic benefit-risk evaluation documents.

Summary of the RMP
The MAH has satisfactory responded to the questions raised and updated the RMP accordingly. The submitted Risk Management Plan, version 1.1 signed 19-06-2018 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Quetiapine Orion (mother product) approved in FI/H/607/04/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Quetiapin Orion, is found adequate. There are no objections to approval of Quetiapin Orion, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Quetiapin Orion, 25 mg, 100 mg, 200 mg and 300 mg, film-coated tablet was positively finalised on 2018-12-20.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se