Public Assessment Report

Scientific discussion

Quetiapin "Sandoz"
100 mg, 150 mg, 200 mg, 300 mg and 400 mg film-coated tablets

Quetiapine (as quetiapine fumarate)

DK/H/1527/001-005/DC

This module reflects the scientific discussion for the approval of Quetiapin "Sandoz". The procedure was finalised on 25 September 2009. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Quetiapin "Sandoz" 100 mg, 150 mg, 200 mg, 300 mg and 400 mg film-coated tablets, from Sandoz A/S. The product was authorised in Denmark on 4 December 2009. The product is indicated for:

- Treatment of schizophrenia.
- Treatment of moderate to severe manic episodes.
- Treatment of major depressive episodes in bipolar disorder.

Quetiapine is not indicated for the prevention of recurrence of manic or depressive episodes.

Quetiapine is a substance with atypical antipsychotic activity, which interacts with a broad sepctrum of neurotransmitter receptors. Quetiapine exhibits affinity to cerebral serotoninergic ($5HT_2$) and dopaminergic D_1 and D_2 receptors. It is assumed that this combination of a receptor antagonist with high selectivity for $5HT_2$ compared with D_2 receptors is responsible for the antipsychotic properties and the less pronounced extrapyrimidal motor side effect profile of quetiapine.

This decentralised procedure concerns a generic/hybrid application. The originator product is Seroquel film-coated tablets from Astra Zeneca UK Limited, registered in the United Kingdom since 31 July 1997. Seroquel film-coated tablets have been registered in Denmark since 19 June 2001 by AstraZeneca A/S.

The applications are submitted according to Article 10.1 (generic application) or 10.3 (hybrid application) depending on the strength and the member state concerned.

II. QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 100 mg, 150 mg, 200 mg, 300 mg and 400 mg of quetiapine (as quetiapine fumarate), respectively.

The 100 mg tablets are yellow, round (8.8 mm diameter) film-coated tablets with score line on one side. The tablet can be divided into equal quarters.
The 150 mg tablets are cream coloured, round (10.5 mm diameter) film-coated tablets with score line on one side. The tablet can be divided into equal halves.
The 200 mg tablets are white, round (11.5 mm diameter) film-coated tablets with score line on one side. The tablet can be divided into equal quarters.
The 300 mg tablets are white, oval (18 mm length and 8.8 mm width) film-coated tablets with score line on one side. The tablet can be divided into equal halves.
The 400 mg tablets are white, round (15.5 mm diameter) film-coated tablets with score line on one side. The tablet can be divided into equal quarters.

The tablets are packed in PVC/COC/PVDC/Aluminium blisters containing 6, 10, 20, 30, 50, 60, 90, 100 or 120 film-coated tablets or in PVC/COC/PVDC/Aluminium perforated unit dose blisters containing 1x100 film-coated tablets. In addition, the tablets are available in HDPE-bottles with PP or PE screw caps with desiccant (silica gel) containing 100, 250 or 500 film-coated tablets. However, not all pack sizes may be marketed.

The excipients in the tablet core are: Calcium hydrogen phosphate dihydrate; cellulose, microcrystalline; lactose monohydrate; magnesium stearate; povidone (K 29/32); silica colloidal hydrated and sodium starch glycolate, type A.

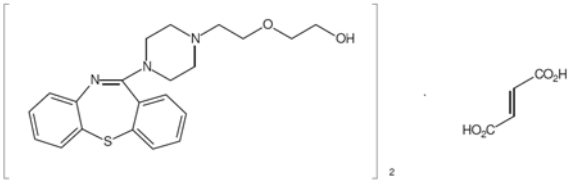
The tablet coating consists of: Hypromellose; lactose monohydrate; macrogol 4000 and titanium dioxide (E 171). In addition the 100 mg and 150 mg film-coated tablets contain iron oxide yellow (E 172).

Compliance with Good Manufacturing Practice
The RMS 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.

II.2 Drug Substance

INN: Quetiapine fumarate
Chemical names:
2-[2-(4-Dibenzo[b,f]-[1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol hemifumarate
11-[4-[2-(2-Hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine hemifumarate
Molecular formula: $(C_{21}H_{25}N_3O_2S)_2 \cdot C_4H_4O_4$
Molecular mass: 883.10 g/mol

Structural formula:



Quetapine fumarate is a white or off-white powder. It is freely soluble in glacial acetic acid and slightly soluble in methanol, acetone and water.

The drug substance quetiapine hemifumarate is not described in any pharmacopoeia.

The documentation on the drug substance is presented as EDMFs from each of the suppliers.
The manufacturing processes of both ASMs have been adequately described in the restricted parts of the EDMFs.
The control tests and specifications for the drug substance product are adequately drawn up.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. Appropriate re-test periods have been set.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

The manufacturing process is a standard process. Adequate validation of the manufacturing process has been performed with pilot scale batches.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on a sufficient number ofbatches of each strength. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Based on the results at long term

and accelerated conditions, a shelf-life of 2 years with no special precautions for storage has been accepted for the drug product.

III. NON-CLINICAL ASPECTS

This product is a generic formulation of Seroquel film-coated tablets, which is 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
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.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Quetiapin "Sandoz" 100 mg film-coated tablets is compared with the pharmacokinetic profile of the bioequivalence reference product Seroquel 100 mg film-coated tablets, AstraZeneca, from the German market..
Biowaivers for the additional strengths have been adequately justified.

The study was an open-label, randomized, three-treatment, three-period, three-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the administrations. 100 mg was administered in each period.

Blood samples were collected pre-dosing and at time points up to 24.0 hours post administration of a single-dose 100 mg film-coated tablet with 240 ml of water for the analyses of quetiapine.

54 healthy male subjects (18-45 years) participated in the study. 50 subjects completed the study and were included in the pharmacokinetic and statistical analysis.
Two subjects dropped out before the second study period; another two subjects dropped out after dosing in period 1.

The pharmacokinetic parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, residual area, K_{el}, $t_{½\ el}$ and MRT.
Primary variables were AUC_{0-t} and C_{max}.

Bioequivalence was assessed based on the 90% geometric confidence interval of the least-squares mean ratio (A/B) of the ln transformed AUC_{0-t} and C_{max} within 80-125%.

Results

TT 8 Primary pharmacokinetic endpoints of quetiapine after an oral single dose of 100 mg quetiapine fumarate (arithmetic mean ± SD, n = 50)

Variable	Stat.	Test	Reference 1	Reference 2
AUC0-tlast [ng*h/ml]	N	50	50	50
	Mean	1415.73	1316.92	1356.71
	SD	504.49	490.64	497.63
Cmax [ng/ml]	N	50	50	50
	Mean	421.42	423.60	413.81
	SD	191.36	180.11	196.15

TT 10 Secondary pharmacokinetic endpoints of quetiapine after an oral single dose of 100 mg quetiapine fumarate (lower and upper ranges, n = 50)

Variable	Stat.	Test	Reference 1	Reference 2
tmax [h]	N	50	50	50
	Mean	0.90	0.97	1.10
	SD	0.58	0.68	0.83
AUC0-inf [ng*h/ml]	N	50	50	50
	Mean	1441.15	1342.02	1382.57
	SD	513.49	504.55	512.88
t½ [h]	N	50	50	50
	Mean	4.12	4.22	4.14
	SD	0.82	0.78	0.90
Kel [1/h]	N	50	50	50
	Mean	0.17	0.17	0.18
	SD	0.04	0.03	0.04
AUC residual area [%]	N	50	50	50
	Mean	1.77	1.75	1.74
	SD	0.94	1.02	1.10

TT 11 90% confidence intervals

Variable	Method	point estimator	confidence intervals	CV (%)
Ratio Test / Reference 1 (n=50)				
AUC0-tlast	ANOVA-log	1.076*	1.020 - 1.135*	16.18 %
Cmax	ANOVA-log	0.984*	0.888 - 1.089*	31.51 %
Ratio Test / Reference 2 (n=50)				
AUC0-tlast	ANOVA-log	1.045*	0.990 - 1.102*	16.18 %
Cmax	ANOVA-log	1.040*	0.938 - 1.152*	31.51 %
*: parametric confidence interval				

The 90% confidence intervals for ln-transformed AUC_{0-t} and C_{max} are within the acceptance range of 80-125%.

Based on the submitted bioequivalence study Quetiapin "Sandoz" 100 mg film-coated tablets are considered bioequivalent with Seroquel film-coated tablets.

The results of the study with the 100 mg formulation can be extrapolated to other strengths, i.e. 150, 200, 300 and 400 mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

The RMS 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).

IV.2 Risk management plan & Pharmacovigilance system

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. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any potential risks occurring either in the Community or in a third country.

Risk Minimisation Plan
In agreement with the EU Risk Management Plan for the inovator product Seroquel the applicant has made a commitment to put special emphasis on close monitoring of:

- quetiapine / methadone drug interaction
- agitation / aggression
- rhabdomyolysis and increased CPK
- hypothyroidism

in the context of routine pharmacovigilance activities concerning quetiapine. Reports regarding the afore mentioned four topics will also be reviewed individually and as an aggregate within PSURs on quetiapine with the PSURs prepared and submitted at 12-monthly intervals. In case any new safety signal regarding the afore mentioned four topics will emerge in between the routine PSUR cycle the applicant will promptly and fully inform the competent authorities concerned.

V. PRODUCT INFORMATION

SmPC and Package leaflet
The content of the SmPC and package leaflet approved during the decentralised procedure is in accordance with that accepted for the reference product Seroquel marketed by AstraZeneca.

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 language used for the purpose of user testing the package leaflet was English. The test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the package leaflet 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

Quetiapin “Sandoz” 100 mg, 150 mg, 200 mg, 300 mg and 400 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Seroquel film-coated tablets from

AstraZeneca. 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 SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other quetiapine containing products.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Quetiapin "Sandoz" with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 25 September 2009. Quetiapin "Sandoz" was authorised in Denmark on 4 December 2009.

A European harmonised birth date has been allocated (1997-07-31) and subsequently the first data lock point for quetiapine is 2008-07. The next PSUR should be submitted with a DLP of 2010-07 and hereafter every 12 months until further notice since a 12 months PSUR cycle applies to the originator product.

The date for the first renewal will be: 22 April 2013.

The following post-approval commitments have been made during the procedure:

1) The MAH commits to inform health care professionals via appropriate methods, addressing the posology, titration and potential adverse events of interest in this indication.

2) The following issues should be monitored and specifically reported upon in the PSURs:
- EPS including TD, somnolence, syncope and orthostatic hypotension including falls and fractures, seizures, agitation/aggression, 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.

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

4) The Applicant should follow, where appropriate and informed, 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.

5) The applicant should follow the same PSUR cycle as applicable for Seroquel. Until further notice PSURs should be provided at 12-monthly intervals based on the International Birth Date for the active substance.

6) Confirmation is given that the stability studies will be continued (at least until the end of the applied shelf-life).

7) Confirmation is given that the first 3 production batches of each strength will be put on stability and tested according to the stability protocol as presented in 3.2.P.8.1.