Public Assessment Report

Scientific discussion

Quetiapin “KRKA”
25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated tablets

Quetiapine (as quetiapine fumarate)

DK/H/1059/001-005/E/001

This module reflects the scientific discussion for the approval of Quetiapin “KRKA”. The repeat use procedure was finalised on 22 February 2010. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

Quetiapin “KRKA” 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated tablets, from KRKA, were first authorised in Denmark on 16 August 2007. Following national approval Denmark acted as reference member state in a decentralised procedure which was finalised on 14 June 2007. Following the first round DCP, the MAH sought recognition of the marketing authorisation by other Member States via a repeat use procedure. This report concerns the 2nd wave MRP.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Quetiapin “KRKA” 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated tablets, from KRKA. The product is indicated for treatment of schizophrenia and for treatment of moderate to severe manic episodes. Quetiapine has not been proved to prevent recurrence of manic or depressive episodes.

Quetiapine fumarate is a dopamine D1-, D2- and 5-HT2 receptor antagonist and belongs to the newer class of the so-called atypical antipsychotics. Quetiapine is used in the medical treatment of schizophrenia and psychotic depression and mania.

Quetiapine exhibits linear pharmacokinetic in the dosing interval. Maximum plasma concentration is reached after 1-1½ hours and the elimination half-life is approximately 7 hours.

This repeat use procedure concerns a generic application claiming essential similarity with the reference product Seroquel 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated tablets registered in the UK since 31 July 1997 by AstraZeneca.

The reference product used for the BE study is Seroquel 25 mg film-coated tablets marketed by AstraZeneca and sourced from the German market.

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC.

The applicant has submitted a compilation of the original dossier for DK/H/1059/001-005/DC along with all responses provided during the procedure.

The present dossier has been updated with regard to any comments addressed during the original procedure (DK/H/1059/001-005/DC) as well as all variations submitted after the end of the DCP. A number of variations have been approved after finalisation of DK/H/1059/001-005/DC.

II. QUALITY ASPECTS

II.1 Introduction

Each Quetiapin “KRKA” film-coated tablet contains 25 mg, 100 mg, 150 mg, 200 mg or 300 mg of quetiapine (as quetiapine fumarate).

The 25 mg tablets are round, pale red film-coated tablets with bevelled edge.
The 100 mg tablets are round, yellow-brown film-coated tablets.
The 150 mg tablets are round, white film-coated tablets with bevelled edge.
The 200 mg tablets are round, white film-coated tablets.
The 300 mg tablets are capsule-shaped, white film-coated tablets.

Quetiapin “KRKA” is packed in blister packs (PVC/Al) in packs of 6 (25 mg tablets only), 10, 20, 30, 30 x 1, 50, 60, 90, 100, 100 x 1, 120 (150 mg and 300 mg tablets only), 180 (150 mg and 300 mg tablets only) or 240 (150 mg and 300 mg tablets only) tablets in a box and in polyethylene (HDPE)
plastic containers in packs of 250 tablets (100 mg and 200 mg tablets only). However, not all pack sizes may be marketed.

The excipients in the tablet core are: Lactose monohydrate; calcium hydrogen phosphate, dihydrate; microcrystalline cellulose (E460); povidone; sodium starch glycolate (type A) and magnesium stearate.

The film-coating consists of: Hypromellose; titanium dioxide (E171); macrogol 4000; yellow iron oxide (E172) (25 mg and 100 mg tablets only) and red iron oxide (E172) (25 mg tablets only).

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

Active Substance: Quetiapine hemifumarate.
INN: Quetiapine
Chemical name(s): 2-[2-(4-Dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol hemifumarate
Molecular formula: C21H25N3O2S.½C4H4O4
Molecular mass: 441.54g/mol

Quetiapine hemifumarate is a white to almost white powder. It is soluble in dimethylformamide >100mg/ml, in methanol > 10mg/ml, in water >1mg/ml. Solubility decreases with increasing pH. It is slightly susceptible to hydrolysis and it is stable in basic and neutral media. Melting point is 172.5-174°C.

X-ray powder diffraction shows that quetiapine hemifumarate manufactured according to the described process crystallizes as one pure crystalline phase.

The product contains quetiapine hemifumarate as active substance which is not monographed in Ph.Eur.
The applicant sources the substance from two suppliers. The documentation from both suppliers is presented in European Drug Master Files in CTD format.

For both EDMFs, sufficient detail is provided showing that potential impurities arising from starting materials are adequately controlled. Specifications are satisfactory and test methods have been presented in adequate detail. Validation data are satisfactory.

The applicant specification for quetiapine hemifumarate reflects parameters and limits applied by both ASMs. All necessary analysis methods and validations are provided. Retest periods of 18 months and 12 months, respectively, with no particular storage precaution have been accepted.
II.3 Medicinal Product

The product composition is adequately described. The development of the product has been satisfactorily performed and explained. No incompatibilities between active and excipients are observed. Excipients are those commonly used for manufacture of a film coated tablet. The packaging materials are standard and shown suitable by the presented stability studies.

Product manufacture is by standard processing and employs a wet granulation process followed by tabletting and film-coating. Manufacture is suitably described. Validation data are provided for three batches of 25 mg tablets at the minimum approved batch size scale. Full validation on the other tablet strengths is not performed as the same equipment and manufacturing conditions are employed. In addition, the formulations of the higher strengths are direct proportional increases of the 25 mg strength. The approach is accepted as the bulk batch size remains the same irrespective of the resultant tablet strength and content of active ingredient in the formulation is reasonably high (>40%). The data provided supports a reproducible product manufacture. A validation plan for the first 3 full scale batches is presented.

The finished product specification is standard for the pharmaceutical form and includes relevant physicochemical, ID, assay and purity tests. Separate release and shelf-life specifications are provided where the latter employ slightly wider related substances limits and includes testing for water content, disintegration and hardness.

Batch analysis data are provided showing compliance with the release requirements and confirming consistency of product manufacture.

Stability data are provided for 3 batches of each strength stored in Al/PVC blisters and for 3 batches each of 100 mg and 200 mg tablets stored in HDPE containers. The approved shelf-life is 2 years with no particular storage precautions. For product packed in HDPE containers, a 3 months in-use shelf-life is approved.

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 since pharmacodynamic, pharmacokinetic and toxicological properties of quetiapine fumarate are well known.

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 fumarate 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 “KRKA” 25 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Seroquel 25 mg film-coated tablets, AstraZeneca, from the German market.

The study was a single centre, open label, randomised, single dose, two-sequence, two-way crossover study conducted under fasting conditions with a wash out period of 7 days between administrations. 25 mg was administered in each period with 240 ml water. Subjects were confined to the clinical research centre from at least 10 hours prior to drug administration until 36 hour post-dose blood draw in each period. Water was permitted ad lib until 1 hour before dosing and again 1 hour after dosing, otherwise ad libitum, otherwise standard meals provided at 4 and 9 hours post dosing and at relevant times thereafter.

Blood sampling performed predosing and at 0.25, 0.5, 0.75, 1, 1.25, 1.50, 1.75, 2.00, 2.5, 3, 4, 6, 8, 12, 16, 24, 30 and 36 hours post-dose in each period.

36 healthy volunteers were randomised into the study and 35 completed (36 males; 20-45 years; 63.4-87.8 kg; all Caucasian). One subject was withdrawn after 6 hour blood draw in period 1 due to low blood pressure.

The pharmacokinetic parameters calculated were AUC_{0-t}, AUC_{0-\infty}, C_{max}, t_{max}, t_1/2. Primary variables were AUC_{0-t}, AUC_{0-\infty} and C_{max}. Secondary parameters were C_{max}/AUC, MRT, t_{max}, t_1/2, and safety.

90% geometric intervals of the ratio (A/B) of least square means from the ln-transformed values for AUC_{0-t}, AUC_{0-\infty} and C_{max} should be within 80-125% in order to conclude bioequivalence. Safety parameters were descriptive only.

**Table 1.** Pharmacokinetic parameters (log-transformed values; arithmetic mean ± SD, t_{max} ± SD, and t_1/2 ±SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} ng.h/ml</th>
<th>AUC_{0-\infty} ng.h/ml</th>
<th>C_{max} ng/ml</th>
<th>t_{max} h</th>
<th>T_{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (S.D.)</td>
<td>108.89 (50.51)</td>
<td>112.26 (51.18)</td>
<td>29.35 (14.74)</td>
<td>1.09 (0.55)</td>
<td>4.77 (1.66)</td>
</tr>
<tr>
<td>Reference (S.D.)</td>
<td>110.45 (45.58)</td>
<td>114.20 (46.36)</td>
<td>28.62 (12.89)</td>
<td>1.01 (0.40)</td>
<td>4.97 (2.12)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>96.80%</td>
<td>88.65-105.70%</td>
<td>96.59%</td>
<td>88.73-105.14%</td>
<td>100.67%</td>
</tr>
<tr>
<td>Intra-subject CV (%)</td>
<td>22.0%</td>
<td>21.2%</td>
<td>30.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter-subject CV (%)</td>
<td>32.88%</td>
<td>31.84%</td>
<td>48.44%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUC_{0-t}, area under the plasma concentration-time curve from time zero to infinity
AUC_{0-\infty}, 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

The 90% confidence intervals for the ln-transformed AUC_{0-t}, AUC_{0-\infty} and C_{max} are within the acceptance range of 80-125%. Calculated intra-subject variabilities are reasonable though for C_{max} appears somewhat on the high side. Based on the submitted bioequivalence study Quetiapin “KRKA” 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated tablets are considered bioequivalent with Seroquel film-coated tablets with respect to rate and extent of absorption of quetiapine. Tolerability of the test product is acceptable and not significantly different from reference product.
A biowaiver for the 100 mg, 150 mg, 200 mg and 300 mg strengths was sought by the applicant and justification, in accordance with section 5.4 of the Bioequivalence guideline, was provided. All requirements are met and a biowaiver is acceptable.

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. The MAH has committed to follow the risk minimisation activities of the innovator (please refer to the commitments listed in section VI). 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.

**V. PRODUCT INFORMATION**

SmPC and Package leaflet

The content of the SmPC and package leaflet approved during the repeat use procedure is in accordance with that accepted for the first round DCP.

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 with 2 participants, 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 “KRKA” 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 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 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 Quetiapine “KRKA” with the reference product, and have therefore granted a marketing authorisation. The repeat use procedure was finished on 22 February 2010.

A European harmonised birth date has been allocated (1997-07-31) The MAH will follow the same PSUR cycle as applicable for Seroquel. Until further notice, PSURs will be provided at 12-monthly intervals based on the International Birth Date for the active substance.

The date for the first renewal will be: 14 June 2012.

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

- With respect to the known stability data of Quetiapine, 25, 100, 150, 200, 300 mg film coated tablets, considering the release specifications of impurities and a reasonable range of expected analytical and manufacturing variability, the MAH proposes to tighten the shelf life limit of total impurities.
  The MAH therefore commits to submit relevant variation within 6 months after the end of the RUP in all MS that were included in the initial DCP as well as in all MS that are included in this RUP.

- Inform health care professionals via appropriate methods, addressing the posology, titration and potential adverse events of interest in the indication “Treatment of bipolar disorder”.

- Monitor and specifically report upon in the PSURs the following issues:
  - 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, hypothryoidism, anaphylaxis, jaundice, hepatitis, increased serum transaminases and gamma-GT, Stevens Johnson syndrome (SJS), neuroleptic malignant syndrome (NMS)
  - Agranulocytosis, cerebrovascular adverse events (CVAEs) inelderly and in nonelderly, 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

- Keep SPC for the product in line with that of the innovator.

- 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.

- Follow the same PSUR cycle as applicable for Seroquel. Until further notice, PSURs will be provided at 12-monthly intervals based on the International Birth Date for the active substance.
• Update of product information (SPC, PL and labelling) according to originator’s product Seroquel (NL/H/156/001-007), submitting Type II variation within 6 months after the end of the RUP.

• Update of product information (SPC, PL and labelling) according to PhVWP core wording on the risk of VTE within 2 months after the end of the RUP:
  According to the new variation regulation (Regulation (EC) No. 1234/2008 effective 1 January 2010), implementation of a PhVWP wording will be submitted as a Type IB variation (no. C.I.3.a).