CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Quetiapin KRKA
Quetiapine (as quetiapine fumarate)

DK/H/1059/009/DC

Date: 07-12-2015

This module reflects the scientific discussion for the approval of Quetiapin KRKA. The procedure was finalised at October 15, 2015. 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 KRKA prolonged-release tablets 50 mg, from Krka Sverige AB.

The product is indicated for:

- treatment of Schizophrenia
- treatment of 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 of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment.
- add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy (see Section 5.1 of the SmPC). Prior to initiating treatment, clinicians should consider the safety profile of Quetiapin KRKA (see Section 4.4 of the SmPC).

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

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines, thiazepines and oxepines.
ATC code: N05A H04
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors.

The pharmacokinetics of quetiapine and norquetiapine are linear and dose-proportional for doses up to 800 mg administered once daily.
Quetiapine prolonged release achieves peak quetiapine and norquetiapine plasma concentrations at approximately 6 hours after administration. The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours.

This decentralised procedure is an extension to DK/H/1059/001-005/DC (film-coated tablets 25 mg, 100 mg, 150 mg, 200 mg, 300 mg). It concerns an abridged application claiming essential similarity to the reference product Seroquel Prolong prolonged-release tablets 50 mg from AstraZeneca A/S, which has been registered in Denmark on January 10, 2008.

The originator product is Seroquel 25 mg film-coated tablets from AstraZeneca B.V., which has been authorised in NL since 1998.

In November 2014 Quetiapin KRKA prolonged-release tablets 150 mg, 200 mg and 300 mg were approved via DK/H/1059/006-008/DC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

The marketing authorization has been granted with condition pursuant to Article 21a, reference is made to section VI of this report.

II. QUALITY ASPECTS

II.1 Introduction

Each prolonged-release tablet contains 50 mg of quetiapine.

The 50 mg prolonged-release tablets are white to almost white, capsule shaped, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark 50 on one side of the tablet. Tablet dimensions: length is 16.2 mm and thickness is 4.0 – 5.2 mm.

The tablets are packed in OPA/Alu/PVC/Alu blisters in pack sizes of 10, 30, 50, 60, 90 and 100 prolonged-release tablets. However, not all pack sizes may be marketed.

Excipients of the tablet core are: Hypromellose, lactose monohydrate, microcrystalline cellulose, sodium citrate dihydrate and magnesium stearate.

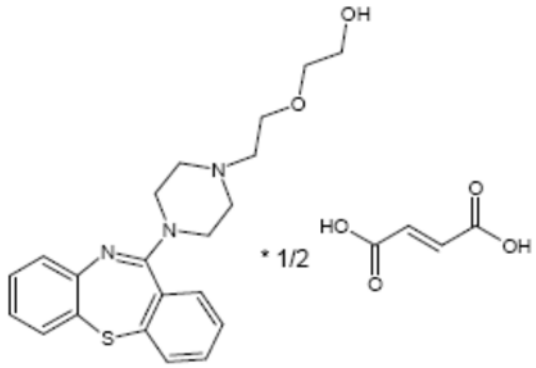
Excipients of the tablet coating are: Hypromellose, titanium dioxide (E171) and macrogol.

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 2.2Drug Substance

INN: Quetiapine
USAN: Quetiapine fumarate
Chemical name(s): i) 2-[2-(4-Dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol hemifumarate
ii) Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, (E)-2-butenedioate (2:1) salt
CAS registry no.: 111974-72-2

Molecular formula: $C_{21}H_{25}N_3O_2S.½C_4H_4O_4$
Structural formula:



Molecular mass: 441.54g/mol

The control tests and specifications for drug substance are in line with the Ph. Eur. monograph. Additional analytical methods for the determination of residual solvents (ethanol, toluene, benzene), *N*,*N*-dimethylaniline, 2-(2-chloroethoxy)ethanol and nickel have been implemented for KRKA material.

Stability studies have been performed with the drug substance. No significant changes in any parameters have been observed.

Acceptable retest period/storage condition: 3 years when stored in the original packaging material.

II.3 Medicinal Product

The development of the drug product has been described, the choice of excipients has been justified and their functions explained. None of the excipients are produced from materials of human or animal origin.

The process validation data provided for the manufacture of the drug product is acceptable.

The control tests and specifications for drug product are adequately drawn up. The drug product specification covers appropriate parameters for this dosage form. Acceptable validation data of the analytical methods has been presented.

Batch analysis has been performed on three smaller production scale batches and three larger production scale batches.

The conditions used in the stability studies are according to ICH stability guidance.

Acceptable shelf-life/storage condition: 2 years/Store in the original packaging in order to protect from moisture/This medicinal product does not require any special temperature storage conditions.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The active substance and the finished product have been adequately described.
From a quality point of view, the benefit/risk ratio of the product is considered positive.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Quetiapine is a well-known active substance with established efficacy and tolerability. As quetiapine is a widely used, well-known active substance, the MAH has no provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview is refers 86 publications up to year 2014.
The non-clinical overview on the clinical pharmacology, efficacy and safety is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Quetiapin KRKA is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

No new studies have been performed.
Quetiapine is already used in existing marketed products and no significant increase in environmental exposure is anticipated as the current application is for a generic product.

From a non-clincial point of view, the benefit/risk ratio of the product is considered positive.

IV. CLINICAL ASPECTS

IV.1 Introduction

Quetiapine is a well-known active substance with established efficacy and tolerability. As quetiapine is a widely used, well-known active substance, the MAH has no provided additional studies (apart from the bioequivalence studies referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical overview refers 50 publications up to year 2014. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

To support this application, the applicant has submitted as report three bioequivalence studies comparing Quetiapin KRKA 50 mg prolonged-release tablets with Seroquel SR 50 mg prolonged-release tablets, AstraZeneca UK Ltd. from the Slovenia market.

Bioequivalence study no. 1

The study was a comparative, single-dose, 2-way cross-over bioavailability study of quetiapine 50 mg prolonged-release tablets and Seroquel® SR 50 mg prolonged-release tablets in healthy volunteers under fasting conditions with a wash out period of 7 days between the two administrations. 50 mg was administered in each period.

The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, residual area, t_{max}, $t_{½}$ and K_{el}. Samples from 50 subjects were analysed and included in the pharmacokinetic evaluation.

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

Treatment	AUC_{0-t} xg/ml/h	$AUC_{0-\infty}$ xg/ml/h	C_{max} xg/ml	t_{max} h	$T_{1/2}$ h
Test	528.58±207.28	552.10±225.22	41.06±16.52	6.81 (1.00, 12.00)	6.76 (4.34, 11.57)
Reference	555.50±244.24	584.03±285.91	39.97±17.04	7.70 (2.00, 14.00)	6.83 (3.63, 16.91)
***Ratio (90% CI)**	96.23% (91.13%-101.62%)	95.94% (90.76%-101.41%)	103.24% (94.88%-112.34%)	-	-
CV (%)	16.3%	-	25.6%	-	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}

C_{max} Maximum plasma concentration

t_{max} Time until Cmax is reached

**ln-transformed values*

Bioequivalence study no. 2

The study was a comparative, randomised, single-dose, 2-way cross-over bioavailability study of quetiapine 50 mg prolonged-release tablets and Seroquel® SR 50 mg prolonged-release tablets in healthy adult volunteers under fed conditions with a wash out period of 7 days between the two administrations. 50 mg was administered in each period.

The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, residual area, t_{max}, $t_{½}$ and K_{el}. Samples from 49 subjects were analysed and included in the pharmacokinetic evaluation.

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

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	609.24±211.39	620.78±219.92	94.08±34.32	4.50 (2.00, 10.00)	5.83 (3.46, 8.72)
Reference	620.80±230.39	634.60±241.42	86.84±31.16	5.00 (2.00, 10.00)	5.96 (3.25, 9.08)
***Ratio (90% CI)**	99.14% (94.25%-104.28%)	98.86% (94.00%-103.98%)	107.50% (101.08%-114.33%)	-	-
Intra-subject CV (%)	15.0%	-	18.3%	-	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until C_{max} is reached

**ln-transformed values*

Bioequivalence study no. 3

The study was a comparative, randomised, multiple-dose, 2-way crossover bioavailability study of quetiapine 50 mg prolonged-release tablets and Seroquel® SR 50 mg prolonged-release tablets in healthy adult volunteers under fasting conditions. 50 mg was administered in each period for 6 consecutive days without a wash out period.

The parameters calculated were $AUC_{0-\tau, ss}$ (dosing interval: 24 hours), $C_{max,ss}$, $C_{min,ss}$, $T_{max,ss}$, C_{av} and C_{pd} %fluctuation on individual plasma profiles. Samples from 54 subjects were analysed and included in the pharmacokinetic evaluation.

Table 2. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment	$AUC_{0-\tau}$ ng/ml/h	$C_{max,ss}$ ng/ml	$C_{min,ss}$ ng/ml	$t_{max,ss}$ h
Test	801.90±276.62	63.66±23.45	11.80±5.22	7.5 (1.0, 13.0)
Reference	761.84±266.03)	60.70±26.76)	12.27±5.38	5.5 (1.00, 11)
***Ratio (90% CI)**	105.96% (100.53%-111.69%)	108.07% (97.92%-119.26%)	99.34% (88.40%-111.63%)	-
Intra-subject CV%	16.4%	31.3%	37.4%	-

$AUC_{0-\tau}$ Area under the plasma concentration curve during a dosage interval at steady state
$C_{max,ss}$ Maximum plasma concentration at steady state
$C_{min,ss}$ Minimum plasma concentration at steady state
$t_{max,ss}$ Time until $C_{max,ss}$ is reached

**ln-transformed values*

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Quetiapin KRKA 50 mg prolonged-release tablets is considered bioequivalent with Seroquel Prolong 50 mg prolonged-release tablets.

IV.3 Summary Pharmacovigilance system

Signed Summary of the MAH's Pharmacovigilance System has been submitted as part of this decentralised procedure. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, 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 KRKA.

The submitted Risk Management Plan, version 1.6, signed August 21, 2015 is considered acceptable.

The summary table of safety concerns and the summary table of risk minimisation measures are included below.

Summary of safety concerns	
Important identified risk	• Neuroleptic malignant syndrome • Neutropenia • QT prolongation • Venous thromboembolism • Pancreatitis • Intestinal obstruction • Extrapyramidal symptoms • Tardive dyskinesia • Somnolence • Syncope and orthostatic hypotension • Seizures • Agranulocytosis • Weight gain • Lipid changes (increased cholesterol, increased triglycerides, or decreased HDLs) • Hyperglycemia and diabetes mellitus • Metabolic risk factors, metabolic syndrome • Syndrome of inappropriate antidiuretic hormone (SIADH) and hyponatremia • Hypothyroidism • Hyperprolactinemia • Hepatitis with or without jaundice • Anaphylactic reaction • Stevens-Johnson syndrome • Withdrawal (discontinuations) symptoms • Dysphagia • Increased blood pressure in pediatric patients
Important potential risks	• Cerebrovascular AEs in elderly patients • Cerebrovascular AEs in the non-elderly patients • Ischemic heart disease

Summary of safety concerns	
	• Increased mortality in elderly demented patients • Aggression/agitation • Abuse and misuse • Suicide and suicidality • Accidental injury • Aspiration pneumonia • Potential for off label and misdosing • Torsade de Pointes • Use in elderly patients
Missing information	• Pregnant or lactating women • Patients on concomitant cardiovascular medications • Patients on concomitant valproic acid

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Neuroleptic malignant syndrome	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Neutropenia	SmPC Section 4.4, 4.8 and 5.1 Other routine risk minimisation measures Prescription only medicine	None proposed
QT prolongation	SmPC Section 4.4, 4.5, 4.8 and 4.9 Other routine risk minimisation measures Prescription only medicine	None proposed
Venous thromboembolism	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Pancreatitis	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Intestinal obstruction	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Extrapyramidal symptoms	SmPC Section 4.2, 4.4, 4.6, 4.8 and 5.1 Other routine risk minimisation measures Prescription only medicine	Educational material
Tardive diskinesia	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Somnolence	SmPC Section 4.2, 4.4, 4.6, 4.7 and 4.8 Other routine risk minimisation measures Prescription only medicine	Educational material
Syncope and orthostatic hypotension	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Seizures	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Agranulocytosis	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed

Weight gain	SmPC Section 4.4, 4.8 and 5.1 Other routine risk minimisation measures Prescription only medicine	Educational material
Lipid changes (increased cholesterol, increased triglycerides, or decreased HDLs)	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	Educational material
Hyperglycemia and diabetes mellitus	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	Educational material
Metabolic risk factors, metabolic syndrome	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	Educational material
Syndrome of inappropriate antidiuretic hormone (SIADH) and hyponatremia	SmPC Section 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Hypothyroidism	SmPC Section 4.4, 4.8 and 5.1 Other routine risk minimisation measures Prescription only medicine	None proposed
Hyperprolactinemia	SmPC Section 4.4, 4.8 and 5.1 Other routine risk minimisation measures Prescription only medicine	None proposed
Hepatitis with or without jaundice	SmPC Section 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Anaphylactic reaction	SmPC Section 4.3 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Stevens-Johnson syndrome	SmPC Section 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Withdrawal (discontinuations) symptoms	SmPC Section 4.4, 4.6 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Dysphagia	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Increased blood pressure in pediatric patients	SmPC section 4.2, 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Cerebrovascular AEs in elderly patients	SmPC Section 4.4 Other routine risk minimisation measures Prescription only medicine	None proposed
Cerebrovascular AEs in the non-elderly patients	The relatedness of Cerebrovascular AEs in the non-elderly patients to quetiapine administration has not been confirmed yet	None proposed
Torsade de Pointes	SmPC Section 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Ischemic heart disease	The relatedness of ischemic heart disease to quetiapine administration has not been confirmed yet.	None proposed

Increased mortality in elderly demented patients	SmPC Section 4.4 Other routine risk minimisation measures Prescription only medicine	None proposed
Aggression/agitation	SmPC Section 4.6 and 4.9 Other routine risk minimisation measures Prescription only medicine	None proposed
Abuse and misuse	The relatedness of abuse and misuse to quetiapine administration has not been confirmed yet.	None proposed
Suicide and suicidality	SmPC Section 4.4 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Accidental injury	SmPC Section 4.4 Other routine risk minimisation measures Prescription only medicine	None proposed
Aspiration pneumonia	SmPC Section 4.4 Other routine risk minimisation measures Prescription only medicine	None proposed
Potential for off label and misdosing	SmPC Section 4.1 and 4.2 Other routine risk minimisation measures Prescription only medicine	None proposed
Use in elderly patients	SmPC Section 4.2, 5.1 and 5.2 Other routine risk minimisation measures Prescription only medicine	None proposed
Pregnant or lactating women	SmPC Section 4.6 and 4.8 Other routine risk minimisation measures Prescription only medicine	None proposed
Patients on concomitant cardiovascular medications	SmPC Section 4.5 Other routine risk minimisation measures Prescription only medicine	None proposed
Patients on concomitant valproic acid	SmPC Section 4.5 Other routine risk minimisation measures Prescription only medicine	None proposed

IV.5 Discussion on the clinical aspects

No new studies have been performed this is considered acceptable as abridged applications, like this procedure, avoid the need for repetitive tests on animals and humans. Reference to the safety and efficacy of the reference product is acceptable as bioequivalence with the reference product has been demonstrated.

V. USER CONSULTATION

In order to comply with Articles 59(3) and 61(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC the applicant has submitted a justification for applying the approved bridging report for Quetiapin KRKA prolonged-release tablets 150 mg, 200 mg and 300 mg (approved via DK/H/1059/006-008/DC). The justification is accepted, the applicant has demonstrated sufficiently that the package leaflet of Quetiapin KRKA prolonged-release tablets 50 mg is legible, clear and easy to use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Quetiapin KRKA 50 mg prolonged-release tablets have a proven chemical-pharmaceutical quality and is a generic form of Seroquel Prolong. Seroquel Prolong 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 that of the brand leader product Seroquel Prolong, except for any product specific information.

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 KRKA with the reference product, and have therefore granted a marketing authorisation.
The decentralised procedure was finalised on October 15, 2015. Quetiapin KRKA was authorised in the RMS on 26-11-2015.

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

Common renewal date will be November 25, 2019.

Post approval commitments not falling under Article 21a/22 of Directive 2001/83/EC were not made during the procedure.

The following conditions pursuant to Article 21a or 22 of Directive 2001/83/EC have been issued:

<u>Additional risk minimisation measures</u>
Additional measures in the form of health care professional educational materials are necessary for the following safety concerns:

- Extrapyramidal symptoms
- Somnolence
- Weight gain

- Lipid changes (increased cholesterol, increased triglycerides, or decreased HDLs)
- Hyperglycemia and diabetes mellitus
- Metabolic risk factors, metabolic syndrome

As duplication of materials on the market place is counterproductive, the decision on whether or not these materials must be distributed in the various markets is to be decided individually by each relevant member state authority for their own market.