Public Assessment Report

Scientific discussion

Stadaquel
Quetiapine (as quetiapine fumarate)

DK/H/1627/001-005/MR

This module reflects the scientific discussion for the approval of Stadaquel. The procedure was finalised on 12 February 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 Stadaquel 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated tablets, from Stada Arzneimittel AG. The date of authorisation was on 18 January, 2008 in Denmark.
The product is indicated for
Treatment of schizophrenia.
Treatment of moderate to severe manic episodes.
Treatment of major depressive episodes in bipolar disorder.
Stadaquel is not indicated for the prevention of recurrence of manic or depressive episodes.

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

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

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 scizophrenia 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.

II. QUALITY ASPECTS

II.1 Introduction

Stadaquel 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated tablets contains as active substance 25 mg, 100 mg, 150 mg, 200 mg and 300 mg quetiapine (as quetiapine fumarate).

The 25 mg tablets are peach coloured, round, biconvex film-coated tablets.
The 100 mg tablets are yellow coloured, round, biconvex film-coated tablets with a score line on one side. The tablet can be divided into equal halves.
The 150 mg tablets are pale yellow coloured, round, biconvex film-coated tablets.
The 200 mg tablets are white, round, biconvex film-coated tablets.
The 300 mg tablets are white, capsule shaped, film-coated tablets with a score line on one side. The tablet can be divided into equal halves.

Stadaquel is packed in PVC/PE/PVdC/Aluminium blisters and in HDPE bottles with PP closure.

The excipients in the tablet core are: Calcium hydrogen phosphate, anhydrous; lactose monohydrate; cellulose, microcrystalline; sodium starch glycollate (Type A); povidone K 27 -32 and magnesium stearate.

The coating consists of: Hypromellose; titanium dioxide (E 171); macrogol 400; iron oxide yellow (E 172) (25 mg, 100 mg and 150 mg only) and iron oxide red (E 172) (25 mg 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

The active substance quetiapine fumarate is not monographed in the Ph.Eur. The applicant sources the substance from two suppliers. The documentation is presented in European Drug Master Files. Synthesis, specifications and methods are all satisfactorily described.

The applicant specification for quetiapine fumarate reflects parameters and limits applied by both ASMs with additional tests for particle size distribution and apparent volume in order to guarantee an optimal performance of the drug product, especially with regard to drug release. The specification is satisfactory and complies with general ICH for drug substance specifications. All necessary analysis methods and validations are provided. A retest period of 30 months and 2 years, respectively is accepted.

II.3 Medicinal Product

The product composition is adequately described. The development of the product has been satisfactorily performed and explained. Drug substance particle size is controlled to ensure a satisfactory dissolution profile. Compatibility with excipients has been demonstrated and is supported by the stability data. Excipients are otherwise common 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. The maximum approved batch size common blend provides a variety of possible tablet batch sizes of each strength. Validation data on batches of maximum batch size common blend compressed to the different tablet strengths are provided and show that reproducibility is achieved.

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, though with the same limits applied for the various parameters. Batch analysis data on a total of 11 batches (all strengths covered) prepared from different common blends have been provided showing compliance with the release requirements and confirming consistency of product manufacture.

Stability data are provided for 11 pilot scale batches stored in the two different proposed market packagings. A shelf-life of 3 years with no particular storage conditions is approved. Tablets stored in bulk packs are shown stable for up to 6 months when stored at 25°C/60% RH in double polyethylene bags /HDPE containers.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of quetiapine fumarate are well known and on this basis, the applicant has not provided additional studies and none are required. An overview based on a literature review, as presented, is therefore appropriate and acceptable.

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 a bioequivalence study in which the pharmacokinetic profile of the test product Stadaquel 25 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Seroquel 25mg film-coated tablets from AstraZeneca from the German market.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The study was a single centre, open label, randomised, single dose, 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 24 hour post-dose blood draw in each period. Water was permitted ad lib until 2 hours before dosing and again 2 hours after dosing, otherwise *ad libitum*.
Blood sampling performed predosing and at 0.333, 0.667, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.0, 12.0, 16.0 and 24.0 hours post-dose in each period. 48 healthy volunteers were randomised into the study and 40 completed (20 males/28 females; 18-55 years; 46.1-93.4 kg; 2 black/37 Caucasian/9 American Hispanic).
Subjects 17 and 37 elected to withdraw prior to drug administration in period 1. Their randomisations were not re-allocated. Subjects 13, 14, 15, 20 and 24 withdrew for personal reasons prior to period 2 drug administration, subjects 9 and 26 after period 1 drug administration due to personal reasons and subject 36 due to AEs in period 2.

Results

Pharmacokinetic parameters (log-transformed values; arithmetic mean ± SD, t_{max} ± SD, and t½ ±SD)

N=40

Treatment	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	238.61	245.72	67.50	1.05	4.75
(S.D.)	(128.85)	(134.16)	(40.06)	(0.62)	(1.12)
Reference	230.54	237.21	62.63	1.08	4.74
(S.D.)	(113.65)	(117.23)	(34.44)	(0.42)	(1.22)
***Ratio (90% CI)**	99.29% 93.59-105.34%	99.34% 93.72-105.29%	103.31% 95.35-111.94%		
Intra-subject CV (%)	13.62%	13.40%	18.55%		
Inter-subject CV (%)	60.56%	60.32%	64.44%		

$AUC_{0-\infty}$ 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

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

Based on the submitted bioequivalence study Stadaquel 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated tablets are considered bioequivalent with Seroquel 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.

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 fumarate 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 fumarate 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 a 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 mutual recognition procedure is in accordance with that accepted for the reference product Seroquel marketed by AstraZeneca..
Moreover, the SmPC is aligned with SmPCs approved via the following DCP procedures: DK/H/1020-1024, 1028, 1052, 1085-1086, 1103/001-006/DC. These procedures were positively ended on 24 June 2007.

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 German. 20 test persons aged 49 to 74 years were included in the testing. The test was based on a questionnaire with 15 questions covering the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.
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

Stadaquel 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Seroquel. 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 Stadaquel with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 12 February 2009.

A European harmonised birth date has been allocated 1997-07-31. First DLP after 30 October 2005: 2006-07.

The date for the first renewal will be: 18 January 2013.

There were no post-approval commitments made during the procedure.