

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-172s000

CHEMISTRY REVIEW(S)

NDA 22-172

**Quetiapine fumarate
SEROQUEL XRTM
50, 200, 300, & 400 mg Tablets**

AstraZeneca

Prafull Shiromani, Ph.D.

**Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	Error! Bookmark not defined.

Chemistry Review Data Sheet

1. NDA 22-172
2. REVIEW #: 1
3. REVIEW DATE: 29-Aug-2007
4. REVIEWER: Prafull Shiromani, Ph.D.
5. PREVIOUS DOCUMENTS: None

6. SUBMISSION BEING REVIEWED:

Submission(s) Reviewed
NDA 22-172

Document Date
22-JAN-2007

7. NAME & ADDRESS OF APPLICANT:

Name: AstraZeneca UK Limited
Address: Alderley Park, Macclesfield, Cheshire, SK 10
4TG, England
Representative: AstraZeneca Pharmaceuticals LP (Mr. Gerald
Limp), Wilmington, DE 19803-8355
Telephone: (302) 886-8017

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: SEROQUEL XRTM
- b) Non-Proprietary Name (USAN): quetiapine fumarate
- c) Code Name/# (ONDC only): ICI 204,636, ZD5077; ZM 204,636
- d) Chem. Type/Submission Priority (ONDC only):

Chemistry Review Data Sheet

- Chem. Type: Type 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Schizophrenia.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 50, 200, 300, & 400 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

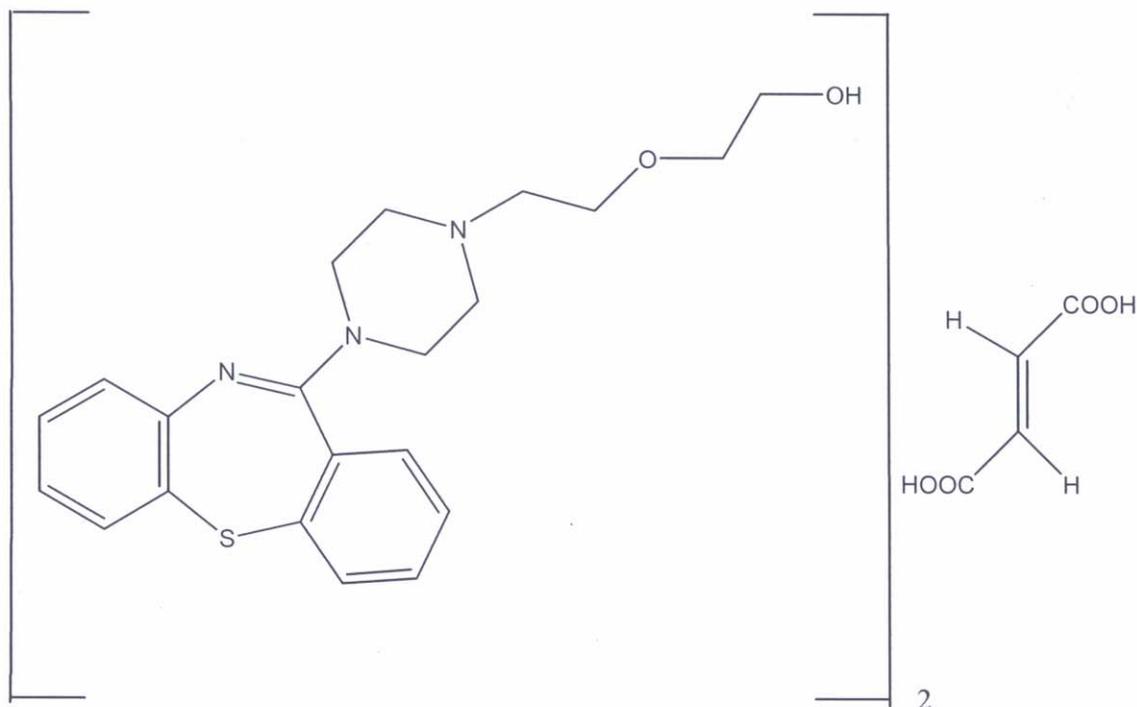
Chemistry Review Data Sheet

2-[2-(4-(Dibenzo[b,f][1,4]thiazepin-11-yl-1-piperaziny-1)ethoxy)ethanol fumarate (2:1) (salt)

Molecular formula: $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$

MW: 883.11

CAS: 111974-72-2



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: N/A

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS

¹ Action codes for DMF Table:
1 – DMF Reviewed.

Chemistry Review Data Sheet

Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
CMC Review 1	NDA 22-047 (25-APR-2007)	Product Approved
CMC Review 2	NDA 22-047 Amendment (09-MAY-2007)	Product Approved

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	None
EES	Acceptable	03-APR-2007	J. D. Ambrogio
Pharm/Tox	N/A	N/A	None
Biopharm	N/A	N/A	None
DMETS	N/A	N/A	None
Methods Validation	N/A	N/A	None
OPDRA	N/A	N/A	None
EA	Acceptable	20-Aug-2007	R. A. Bloom
Microbiology	N/A	N/A	None

The Chemistry Review for NDA 22-172

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for **Approval** from a CMC perspective. This NDA has no CMC and all the CMC has been referenced to NDA 22-047 – SEROQUEL XR Extended-Release Tablets, 50, 200, 300, & 400 mg Tablets for the treatment of Schizophrenia in adults, which was approved by FDA on May 17, 2007.

The overall evaluation from the Office of Compliance for cGMP compliance is **ACCEPTABLE**.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

SEROQUEL XR tablets will be supplied as biconvex, film coated, capsule-shaped tablets containing 50, 200, 300 or 400 mg quetiapine fumarate (expressed as free base) packed in both HDPE bottles, with child resistant closures, and clear (b)(4) blister packs. The 4 strengths are differentiated by size, color (50 mg- (b)(4), 200 mg-yellow, 300 mg-pale yellow, and 400 mg-white), and intagliation.

The drug substance is present in the tablets as the fumarate salt and all doses and tablet strengths are expressed as milligrams of base, not as fumarate salt.

SEROQUEL IR has been previously formulated as immediate release orally administered 25, 50, 100, 150, 200, 300 and 400mg tablets. These may be dosed either 2 or 3 times daily. A sustained release formulation has been developed to provide a once daily dosing regimen, so as to improve patient compliance and be beneficial clinically.

Chemistry Review Data Sheet

SEROQUEL SR

(b) (4)

SEROQUEL^{(b) (4)} 50, 200, 300 and 400 mg tablets, have been studied for stability under ICH conditions. The 24-month stability data support a shelf life of 36 months (ref. ICH Q1E) for all strengths in all commercial packages when stored at 25°C.

A Biopharm Review concluded that the sponsor's dissolution methodology and the IVIVC A are acceptable.

An Environmental Assessment and Finding Of No Significant Impact for this product was prepared by Dr. Raanan Bloom (OPS/IO/PARS) on 20-Aug-2007. This assessment indicates that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration and since no adverse effects are expected no further testing is required.

Drug Substance

The drug substance for the sustained release formulation remains unchanged compared to that (quetiapine fumarate) approved for NDA 20-639 for SEROQUEL immediate release tablets.

B. Description of How the Drug Product is Intended to be Used

SEROQUEL^{(b) (4)} is a psychotropic agent indicated for ^{(b) (4)} Schizophrenia. It is to be administered once daily, preferably in the evening. The recommended initial dose is 300 mg/day. The effective dose range is 400-800 mg per day depending on the response and tolerance of the individual patient. Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day. It is recommended that the tablets be taken without food or with a light meal. The tablets should be swallowed whole and not split, or chewed or crushed.

Chemistry Review Data Sheet

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (22-172) is recommended for **APPROVAL**.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Prafull Shiromani Ph.D.

ChemistryTeamLeaderName/Date Ramesh Sood, Ph.D.

ProjectManagerName/Date Kimberly Updegraff

C. CC Block

**2 Page(s) has been Withheld in Full following this page as
B4 (CCI/TS)**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Prafull Shiromani
8/30/2007 02:12:06 PM
CHEMIST

Ramesh Sood
8/30/2007 02:46:41 PM
CHEMIST

Initial Quality Assessment Branch I

OND Division: Division of Psychiatry Products
NDA: 22-172
Applicant: AstraZeneca
Letter Date: 05-MAR-07
Stamp Date: 06-MAR-07
PDUFA Date: 06-JAN-08
Trademark: Seroquel® (b) (4)
Established Name: Quetiapine Fumarate
Dosage Form: Extended release tablets (50, 200, 300, 400 mg)
Route of Administration: Oral
Indication: (b) (4) schizophrenia patients
Assessed by: Thomas F. Oliver, Ph.D.

Summary

Seroquel® was approved for the treatment of schizophrenia on September 26, 1997. AstraZeneca has submitted Seroquel® (quetiapine fumarate) (b) (4) Tablets for the treatment of schizophrenia (NDA 22-047, currently under review). AstraZeneca has just submitted NDA 22-172 for (b) (4) schizophrenia. All CMC information is cross-referenced to NDA 22-047. Please refer to the IQA for NDA 22-047.

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. As Dr. Wendy Wilson and Dr. Prafull Shiromani are currently reviewing NDA 22-047 (Seroquel (b) (4)), they would be prudent choices to work on this NDA. The sponsor has **submitted an EA**, which will need to be consulted for review. All sites have been submitted into EES (08-MAR-07), however, these sites will need to be verified by the reviewers.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Oliver
3/8/2007 09:42:30 AM
CHEMIST

Ramesh Sood
3/8/2007 04:32:33 PM
CHEMIST