

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 22-047/S-011**

***Trade Name:*** Seroquel XR

***Generic Name:*** quetiapine fumarate

***Sponsor:*** AstraZeneca

***Approval Date:*** December 2, 2009

***Indication:*** Adjunctive therapy in the treatment of Major Depressive Disorder (MDD)

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

**APPROVAL LETTER**



NDA 022047/S-011/S-016/S-017/S-019/S-022

**SUPPLEMENT APPROVAL**

AstraZeneca  
Attention: Pat Patterson  
Director, Regulatory Affairs  
1800 Concord Pike  
P.O. Box 15437  
Wilmington, DE 19850-5437

Dear Ms. Patterson:

Please refer to your supplemental new drug application dated February 27, 2008 (S-011) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Seroquel XR (quetiapine fumarate) Extended-Release 50 mg, 150 mg, 200 mg, 300 mg, and 400 mg Tablets.

We acknowledge receipt of your Class 2 resubmission dated June 6, 2009. This submission constituted a complete response to our December 22, 2008 action letter.

This supplemental new drug application (NDA) proposes the following revisions to product labeling:

**S-011 (submitted as an efficacy supplement)**

- Provides for a new indication of adjunctive therapy in the treatment of Major Depressive Disorder (MDD) and respective labeling changes.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We also note that your "Changes Being Effected" supplemental applications submitted on July 11, 2008 (S-017), September 11, 2008 (S-019), December 15, 2008 (S-022), and your "Prior Approval" supplement submitted on December 19, 2007 (S-016) have been superseded by this approval action. We will not review these supplemental applications but they will be retained in our files.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling

(text for the package insert). For administrative purposes, please designate this submission, “SPL for approved NDA 22047/S-011”.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for both children and adolescents. At the present time, there are only two approved treatments for pediatric MDD, fluoxetine and escitalopram, both SSRIs. It is not at all clear what the best approach would be for a nonresponding pediatric patient, but most clinicians would not want to move to adding an atypical antipsychotic. Thus, studies of adjunctive therapy in the treatment of Major Depressive Disorder (MDD) would be highly impractical.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Since Seroquel XR (quetiapine fumarate) was approved on May 17, 1997, we have become aware of additional clinical trial data and postmarketing safety data that show a risk of hyperglycemia, hyperlipidemia, and weight gain associated with all forms of Seroquel XR (quetiapine fumarate) in all patient populations. We consider this information to be “new safety information” as defined in section 505-1(b) of FDCA.

Your proposed REMS, submitted on November 24, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

- a. An evaluation of patients' understanding of the serious risks of SEROQUEL XR (quetiapine fumarate).
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505 (o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022047 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 022047  
PROPOSED REMS MODIFICATION  
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 022047  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important safety related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch  
Food and Drug Administration  
5600 Fishers Lane, Room 12B05  
Rockville, MD 20857

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, email your Regulatory Project Manager at [Juliette.Toure@fda.hhs.gov](mailto:Juliette.Toure@fda.hhs.gov).

Sincerely,  
*{See appended electronic signature page}*  
Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosures  
Content of Labeling  
REMS

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22047

-----  
SUPPL-11

-----  
ASTRAZENECA  
PHARMACEUTICA  
LS LP

-----  
SEROQUEL XR

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN  
12/02/2009

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

**OTHER ACTION LETTERS**



NDA 22-047/S-010/S-011/S-012

**COMPLETE RESPONSE**

Astra Zeneca, Pharmaceuticals LP  
Attention: Gerald L. Limp  
Director, Regulatory Affairs  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Dear Mr. Limp:

Please refer to your supplemental new drug applications (sNDA), dated and received February 27, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel XR (quetiapine fumarate) Extended-Release Tablets.

We acknowledge receipt of your amendments dated June 25, November 6, 2008, and December 8, 2008.

These supplemental new drug applications are intended to support claims for acute monotherapy, acute adjunctive therapy, and maintenance monotherapy in patients with Major Depressive Disorder (MDD).

We have completed the review of your applications and have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

**INADEQUATE INFORMATION REGARDING LONGER-TERM RISKS FOR THE TREATMENT OF MDD**

Although clinical efficacy has been demonstrated for Seroquel XR in the treatment of MDD, the longer term risks of using this drug in the population of patients with MDD have not been adequately addressed in your application. These risks include metabolic risks (hyperglycemia/diabetes, hyperlipidemia, and weight gain) and a risk for tardive dyskinesia. Therefore, we require that these risks be addressed prior to taking a final action on these applications.

A risk benefit analysis will be integral to any discussion of the use of Seroquel XR for common, non-psychotic disorders such as MDD. While MDD is an accepted target for pharmacotherapy,

there are multiple effective therapies approved for the treatment of MDD that do not have the same longer term safety risks. Any argument to support the use of Seroquel XR for the treatment of MDD must address these longer-term risks.

Please submit your arguments and the data to support the use of Seroquel XR for our evaluation. For these longer term risks, you may include data from observational databases, post-marketing data, and literature data elucidating these longer-term risks of using Seroquel XR (i.e., longer-term metabolic effects and any risk of Tardive Dyskinesia associated with Seroquel XR treatment).

## **LABELING**

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously approved labeling changes.

Add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide.**"

## **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

## **OTHER**

Within 1 year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA guidance for industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call LCDR Renmeet Grewal, Pharm. D., Senior Regulatory Project Manager, at (301) 796-1080.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure: Labeling

61 Pages Immediately Following Withheld - b(4) Draft Labeling

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

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Thomas Laughren  
12/22/2008 10:58:35 AM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 22-047/S-011**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use SEROQUEL XR safely and effectively. See full prescribing information for SEROQUEL XR.

**SEROQUEL XR (quetiapine fumarate) Extended-Release Tablets**  
Initial U.S. Approval: 1997

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA** See full prescribing information for complete boxed warning.

- Antipsychotic drugs are associated with an increased risk of death. (5.1)
- Quetiapine is not approved for elderly patients with Dementia-Related Psychoses. (5.1)

**WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS** See full prescribing information for complete boxed warning.

- Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders. (5.2)

-----**RECENT MAJOR CHANGES**-----

- Indications and Usage, Schizophrenia (1.1), 12/2009
- Indications and Usage, Bipolar Disorder (1.2), 12/2009
- Indications and Usage, Major Depressive Disorder (MDD), Adjunctive Treatment with Antidepressants (1.3), 12/2009
- Dosage and Administration, Schizophrenia (2.1), 12/2009
- Dosage and Administration, Bipolar Disorder (2.2), 12/2009
- Dosage and Administration, Major Depressive Disorder (MDD), Adjunctive Treatment with Antidepressants (2.3), 12/2009
- Warnings and Precautions, Hyperglycemia (5.4), 12/2009
- Warnings and Precautions, Hyperlipidemia (5.5), 12/2009
- Warnings and Precautions, Weight Gain (5.6), 12/2009
- Warnings and Precautions, Increases in Blood Pressure (Children and Adolescents) (5.9), 12/2009
- Warnings and Precautions, Hypothyroidism (5.13), 01/2009
- Warnings and Precautions, Hyperprolactinemia (5.14), 01/2009
- Warnings and Precautions, Potential for Cognitive and Motor Impairment (5.16), 12/2009
- Warnings and Precautions, Suicide (5.20), 12/2009

-----**INDICATIONS AND USAGE**-----

- SEROQUEL XR is an atypical antipsychotic indicated for the:
- Treatment of schizophrenia (1.1)
    - Adults: Efficacy was established with SEROQUEL XR in one 6-week and one maintenance trial in patients with schizophrenia as well as in three 6-week trials with SEROQUEL in patients with schizophrenia (14.1)
  - Acute treatment of manic or mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex (1.2)
    - Adults: Efficacy was established with SEROQUEL XR in one 3-week trial in patients with manic or mixed episodes associated with bipolar I disorder as well as two 12-week monotherapy trials and one 3-week adjunctive trial with SEROQUEL in patients with manic episodes associated with bipolar I disorder (14.2)
  - Acute treatment of depressive episodes associated with bipolar I disorder (1.2)
    - Adults: Efficacy was established with SEROQUEL XR in one 8-week trial in patients with bipolar I or II disorder as well as two 8-week trials with SEROQUEL in patients with bipolar I or II disorder (14.2)
  - Maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex (1.2)
    - Adults: Efficacy was established with SEROQUEL in two maintenance trials in patients with bipolar I disorder (14.2)
  - Adjunctive treatment of major depressive disorder (MDD) (1.3)
    - Adults: Efficacy as an adjunct to antidepressants was established in two 6-week trials in patients with MDD who had an inadequate response to an antidepressant alone (14.3)

-----**DOSAGE AND ADMINISTRATION**-----

SEROQUEL XR Tablets should be swallowed whole and not split, chewed or crushed. SEROQUEL XR should be taken without food or with a light meal (approx. 300 calories). SEROQUEL XR should be administered once daily, preferably in the evening.

Schizophrenia-(2.1)	Day 1: 300 mg/day Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day.	400-800 mg/day
Schizophrenia Maintenance (Monotherapy) (2.1)	400 mg/day to 800 mg/day	400-800 mg/day
Bipolar Mania- Acute monotherapy or as an adjunct to lithium or divalproex (2.2)	Day 1: 300 mg. Day 2: 600 mg. Day 3: between 400 mg and 800 mg	400- 800 mg/day
Depressive Episodes Associated with Bipolar Disorder (2.2)	Day 1: 50 mg Day 2: 100 mg Day 3: 200 mg Day 4: 300 mg	300 mg/day
Bipolar I Disorder- Maintenance Treatment as an adjunct to lithium or divalproex (2.2)	400 mg/day to 800 mg/day	400-800 mg/day
Major Depressive Disorder, Adjunctive Therapy with Antidepressants (2.3)	Day 1 and 2: 50 mg Day 3 and 4: 150 mg	150-300 mg/day

\*After initial dosing, adjustments can be made upwards or downwards, if necessary, within the dose range depending upon the clinical response and tolerance of the patient.

-----**DOSAGE FORMS AND STRENGTHS**-----

Extended-Release Tablets: 50 mg, 150 mg, 200 mg, 300 mg, and 400 mg

-----**CONTRAINDICATIONS**-----

None

-----**WARNINGS AND PRECAUTIONS**-----

- Increased Mortality in Elderly Patients with Dementia-Related Psychoses:** Antipsychotic drugs, including quetiapine, are associated with an increased risk of death; causes of death are variable. (5.1)
- Suicidality and Antidepressant Drugs:** Increased the risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders. (5.2)
- Neuroleptic Malignant Syndrome (NMS):** Manage with immediate discontinuation and close monitoring. (5.3)
- Hyperglycemia and Diabetes Mellitus (DM):** Ketoacidosis, hyperosmolar coma and death have been reported in patients treated with atypical antipsychotics, including quetiapine. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. When starting treatment, patients with diabetes or risk factors for diabetes should undergo blood glucose testing before and during treatment. (5.4)
- Hyperlipidemia:** Undesirable alterations in lipids have been observed. Increases in total cholesterol, LDL-cholesterol and triglycerides and decreases in HDL-cholesterol have been reported in clinical trials. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically, during treatment. (5.5)
- Weight Gain:** Patients should receive regular monitoring of weight. (5.6)
- Tardive Dyskinesia:** Discontinue if clinically appropriate. (5.7)
- Orthostatic Hypotension:** Associated dizziness, tachycardia and syncope may occur especially during the initial dose titration period. Use in caution in patients with known cardiovascular or cerebrovascular disease. (5.8)
- Increased Blood Pressure in Children and Adolescents:** Blood pressure should be measured at the beginning of, and periodically during treatment in children and adolescents. SEROQUEL XR has not been evaluated in pediatric patients. (5.9)
- Leukopenia, Neutropenia and Agranulocytosis:** have been reported with atypical antipsychotics including SEROQUEL XR. Patients with a pre-existing low white cell count (WBC) or a history of leukopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months of treatment and should discontinue SEROQUEL XR at the first sign of a decline in WBC in absence of other causative factors. (5.10)
- Cataracts:** Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination is recommended when starting treatment and at 6-month intervals during chronic treatment. (5.11)
- Suicide:** The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high risk patients should accompany drug therapy. (5.20)
- See Full Prescribing Information for additional **WARNINGS and PRECAUTIONS.**

-----**ADVERSE REACTIONS**-----

Indication	Dosing Instructions*	Recommended Dose / Dose Range
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Most common adverse reactions (incidence  $\geq 5\%$  and twice placebo) in decreasing frequency are: somnolence, dry mouth, constipation, dizziness, increased appetite, dyspepsia, weight gain, fatigue, dysarthria, and nasal congestion. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- **P450 3A Inhibitors:** May decrease the clearance of quetiapine. Lower doses of quetiapine may be required. (7.1)
- **Hepatic Enzyme Inducers:** May increase the clearance of quetiapine. Higher doses of quetiapine may be required with phenytoin or other inducers. (7.1)
- **Centrally Acting Drugs:** Caution should be used when quetiapine is used in combination with other CNS acting drugs. (7)
- **Antihypertensive Agents:** Quetiapine may add to the hypotensive effects of these agents. (7)

- **Levodopa and Dopamine Agents:** Quetiapine may antagonize the effect of these drugs. (7)

-----USE IN SPECIFIC POPULATIONS-----

- **Geriatric Use:** Consider a lower starting dose (50 mg/day), slower titration, and careful monitoring during the initial dosing period in the elderly. (2.3 and 8.5)
- **Hepatic Impairment:** Lower starting dose (50 mg/day) and slower titration may be needed. (2.3, 8.7, 12.3)
- **Pregnancy:** Limited human data. Based on animal data, may cause fetal harm. (8.1)
- **Nursing Mothers:** Caution should be exercised when administered to a nursing woman. (8.3)
- **Pediatric Use:** Safety and effectiveness have not been established. (8.4)

**SEE 17 FOR PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE**

**REVISED X**

**[FULL PRESCRIBING INFORMATION: CONTENTS\*  
SUICIDALITY AND ANTIDEPRESSANT DRUGS; WARNING:  
INCREASED MORTALITY IN ELDERLY PATIENTS WITH  
DEMENTIA-RELATED PSYCHOSIS;**

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- 1.1 SCHIZOPHRENIA
- 1.2 BIPOLAR DISORDER
- 1.3 MAJOR DEPRESSIVE DISORDER, ADJUNCTIVE THERAPY WITH ANTIDEPRESSANTS

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- 2.6 SWITCHING PATIENTS FROM SEROQUEL TABLETS TO SEROQUEL XR TABLETS
- 2.7 SWITCHING FROM ANTIPSYCHOTICS

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- 9.2 ABUSE
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- 11 DESCRIPTION**
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- 12.1 MECHANISM OF ACTION
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- 13 NONCLINICAL TOXICOLOGY**
- 13.1 CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
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## FULL PRESCRIBING INFORMATION

### **WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. SEROQUEL XR is not approved for the treatment of patients with dementia-related psychosis [see *Warnings and Precautions* (5.1)].

### **SUICIDALITY AND ANTIDEPRESSANT DRUGS**

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL XR or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL XR is not approved for use in pediatric patients [see *Warnings and Precautions* (5.2)].

## **1 INDICATIONS AND USAGE**

### **1.1 Schizophrenia**

SEROQUEL XR is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL XR in schizophrenia was established in one 6-week and one maintenance trial in adults with schizophrenia as well by

extrapolation from three 6-week trials in adults with schizophrenia treated with SEROQUEL [see *Clinical Studies (14.1)*].

## **1.2 Bipolar Disorder**

SEROQUEL XR is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex. The efficacy of SEROQUEL XR in manic or mixed episodes of bipolar I disorder was established in one 3-week trial in adults with manic or mixed episodes associated with bipolar I disorder as well by extrapolation from two 12-week monotherapy and one 3-week adjunctive trial in adults with manic episodes associated with bipolar I disorder treated with SEROQUEL [see *Clinical Studies (14.2)*].

SEROQUEL XR is indicated for the acute treatment of depressive episodes associated with bipolar disorder. The efficacy of SEROQUEL XR was established in one 8-week trial in adults with bipolar I or II disorder as well as extrapolation from two 8-week trials in adults with bipolar I or II disorder treated with SEROQUEL [see *Clinical Studies (14.2)*].

SEROQUEL XR is indicated for the maintenance treatment of bipolar I disorder, as an adjunct to lithium or divalproex. Efficacy was extrapolated from two maintenance trials in adults with bipolar I disorder treated with SEROQUEL. The effectiveness of monotherapy for the maintenance treatment of bipolar disorder has not been systematically evaluated in controlled clinical trials [see *Clinical Studies (14.2)*].

## **1.3 Adjunctive Treatment of Major Depressive Disorder (MDD)**

SEROQUEL XR is indicated for use as adjunctive therapy to antidepressants for the treatment of MDD. The efficacy of SEROQUEL XR as adjunctive therapy to antidepressants in MDD was established in two 6-week trials in adults with MDD who had an inadequate response to antidepressant treatment [see *Clinical Studies (14.3)*].

## **2 DOSAGE AND ADMINISTRATION**

SEROQUEL XR tablets should be swallowed whole and not split, chewed or crushed.

It is recommended that SEROQUEL XR be taken without food or with a light meal (approximately 300 calories) [see *Clinical Pharmacology (12.3)*].

## 2.1 Schizophrenia

Dose Selection—SEROQUEL XR should be administered once daily, preferably in the evening. The recommended initial dose is 300 mg/day. Patients should be titrated within a dose range of 400 mg/day – 800 mg/day depending on the response and tolerance of the individual patient [see *Clinical Studies (14.1)*]. Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Maintenance Treatment—A maintenance trial in adult patients with schizophrenia treated with SEROQUEL XR has shown this drug to be effective in delaying time to relapse in patients who were stabilized on SEROQUEL XR at doses of 400 mg/day to 800 mg/day for 16 weeks. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [see *Clinical Studies (14.1)*].

## 2.2 Bipolar Disorder

### ***Bipolar Mania***

Usual Dose for Acute Monotherapy or Adjunct Therapy (with lithium or divalproex)

Dose Selection—When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL XR should be administered once daily in the evening starting with 300 mg on Day 1 and 600 mg on Day 2. SEROQUEL XR can be adjusted between 400 mg and 800 mg beginning on Day 3 depending on the response and tolerance of the individual patient.

#### **Recommended Dosing Schedule**

Day	Day 1	Day 2	Day 3
SEROQUEL XR	300 mg	600 mg	400 mg to 800 mg

### ***Depressive Episodes Associated with Bipolar Disorder***

Usual Dose—SEROQUEL XR should be administered once daily in the evening to reach 300 mg/day by Day 4.

#### **Recommended Dosing Schedule**

Day	Day 1	Day 2	Day 3	Day 4
SEROQUEL XR	50 mg	100 mg	200 mg	300 mg

### Maintenance Treatment for Bipolar I Disorder

Maintenance Treatment—Maintenance of efficacy in bipolar I disorder was demonstrated with SEROQUEL (administered twice daily totaling 400 mg/day to 800 mg/day) as adjunct therapy to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [*see Clinical Studies (14.2)*].

## 2.3 Major Depressive Disorder, Adjunctive Therapy with Antidepressants

Dose Selection—SEROQUEL XR in a dose range of 150 mg/day to 300 mg/day was demonstrated to be effective as adjunctive therapy to antidepressants. Begin with 50 mg once daily in the evening. On Day 3, the dose can be increased to 150 mg once daily in the evening. There were dose-dependent increases in adverse reactions in the recommended dose range of 150 mg/day to 300 mg/day. Doses above 300 mg/day were not studied [*see Clinical Studies (14.3)*].

## 2.4 Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions [*see Use in Specific Populations (8.5, 8.7) and Clinical Pharmacology (12)*]. When indicated, dose escalation should be performed with caution in these patients.

Elderly patients should be started on SEROQUEL XR 50 mg/day and the dose can be increased in increments of 50 mg/day depending on the response and tolerance of the individual patient.

Patients with hepatic impairment should be started on SEROQUEL XR 50 mg/day. The dose can be increased daily in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerance of the patient.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital [*see Drug Interactions (7.1)*].

## **2.5 Re-initiation of Treatment in Patients Previously Discontinued**

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting therapy of patients who have been off SEROQUEL XR for more than one week, the initial dosing schedule should be followed. When restarting patients who have been off SEROQUEL XR for less than one week, gradual dose escalation may not be required and the maintenance dose may be reinitiated.

## **2.6 Switching Patients from SEROQUEL Tablets to SEROQUEL XR Tablets**

Patients who are currently being treated with SEROQUEL (immediate release formulation) may be switched to SEROQUEL XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

## **2.7 Switching from Antipsychotics**

There are no systematically collected data to specifically address switching patients from other antipsychotics to SEROQUEL XR, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, if medically appropriate, initiate SEROQUEL XR therapy in place of the next scheduled injection. The need for continuing existing extrapyramidal syndrome medication should be re-evaluated periodically.

## **3 DOSAGE FORMS AND STRENGTHS**

50 mg extended-release tablets  
150 mg extended-release tablets  
200 mg extended-release tablets  
300 mg extended-release tablets  
400 mg extended-release tablets

## **4 CONTRAINDICATIONS**

None

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. SEROQUEL XR (quetiapine fumarate) is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

### **5.2 Clinical Worsening and Suicide Risk**

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

**Table 1**

<b>Age Range</b>	<b>Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated</b>
	<b>Increases Compared to Placebo</b>
<18	14 additional cases
18-24	5 additional cases
	<b>Decreases Compared to Placebo</b>
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

**All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.**

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening

depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

**Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for SEROQUEL XR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

**Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

### **5.3 Neuroleptic Malignant Syndrome (NMS)**

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including quetiapine. Rare cases of NMS have been reported with quetiapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (eg, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central

anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

#### **5.4 Hyperglycemia and Diabetes Mellitus**

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including quetiapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

**Table 2: Fasting Glucose—Proportion of Patients Shifting to  $\geq 126$  mg/dL in short-term ( $\leq 12$  weeks) Placebo Controlled Studies**

Laboratory Analyte	Category Change (At Least Once) from Baseline	Treatment Arm	N	Patients n(%)
Fasting Glucose	Normal to High ( $<100$ mg/dL to $\geq 126$ mg/dL)	Quetiapine	2907	71 (2.4%)
		Placebo	1346	19 (1.4%)
	Borderline to High ( $\geq 100$ mg/dL and $<126$ mg/dL) to $\geq 126$ mg/dL	Quetiapine	572	67 (11.7%)
		Placebo	279	33 (11.8%)

**Adults:**

In a 24-week trial (active-controlled, 115 patients treated with SEROQUEL) designed to evaluate glycemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a treatment-emergent post-glucose challenge glucose level  $\geq 200$  mg/dL was 1.7% and the incidence of a fasting treatment-emergent blood glucose level  $\geq 126$  mg/dL was 2.6%. The mean change in fasting glucose from baseline was 3.2 mg/dL and mean change in 2 hour glucose from baseline was -1.8 mg/dL for quetiapine.

In 2 long-term placebo-controlled randomized withdrawal clinical trials for bipolar maintenance, mean exposure of 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the mean change in glucose from baseline was +5.0 mg/dL for quetiapine and -0.05 mg/dL for placebo. The exposure-adjusted rate of any increased blood glucose level ( $\geq 126$  mg/dL) for patients more than 8 hours since a meal (however, some patients may not have been precluded from calorie intake from fluids during fasting period) was 18.0 per 100 patient years for SEROQUEL (10.7% of patients; n=556) and 9.5 for placebo per 100 patient years (4.6% of patients; n=581).

Table 3 shows the percentage of patients with shifts in blood glucose to  $\geq 126$  mg/dL from normal baseline in MDD adjunct therapy trials by dose.

**Table 3: Percentage of Patients with Shifts from Normal Baseline in Blood Glucose to  $\geq 126$  mg/dL (assumed fasting) in MDD Adjunct Therapy Trials by Dose**

**Table 3**

<b>Laboratory Analyte</b>	<b>Treatment Arm</b>	<b>N</b>	<b>Patients n (%)</b>
Blood Glucose $\geq 126$ mg/dL	Placebo	277	17 (6%)
	SEROQUEL XR 150 mg	280	19 (7%)
	SEROQUEL XR 300 mg	269	32 (12%)

*Children and Adolescents:* Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In a placebo-controlled SEROQUEL monotherapy study of adolescent patients (13–17 years of age) with schizophrenia (6 weeks duration), the mean change in fasting glucose levels for SEROQUEL (n=138) compared to placebo (n=67) was  $-0.75$  mg/dL versus  $-1.70$  mg/dL. In a placebo-controlled SEROQUEL monotherapy study of children and adolescent patients (10–17 years of age) with bipolar mania (3 weeks duration), the mean change in fasting glucose level for SEROQUEL (n=170) compared to placebo (n=81) was  $3.62$  mg/dL versus  $-1.17$  mg/dL. No patient in either study with a baseline normal fasting glucose level ( $<100$  mg/dL) or a baseline borderline fasting glucose level ( $\geq 100$  mg/dL and  $<126$  mg/dL) had a treatment-emergent blood glucose level of  $\geq 126$  mg/dL.

## 5.5 Hyperlipidemia

*Adults:* Undesirable alterations in lipids have been observed with quetiapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using quetiapine is recommended.

Table 4 shows the percentage of patients with changes in cholesterol and triglycerides from normal baseline by indication in clinical trials with SEROQUEL XR .

**Table 4: Percentage of Adult Patients with Shifts in Total Cholesterol, Triglycerides, LDL-Cholesterol and HDL-Cholesterol from Baseline to Clinically Significant Levels by Indication**

**Table 4**

Laboratory Analyte	Indication	Treatment Arm	N	Patients n (%)
Total Cholesterol $\geq$ 240 mg/dL	Schizophrenia <sup>a</sup>	SEROQUEL XR	718	67 (9%)
		Placebo	232	21 (9%)
	Bipolar Depression <sup>b</sup>	SEROQUEL XR	85	6 (7%)
		Placebo	106	3 (3%)
	Bipolar Mania <sup>c</sup>	SEROQUEL XR	128	9 (7%)
		Placebo	134	5 (4%)
Major Depressive Disorder (Adjunct Therapy) <sup>d</sup>	SEROQUEL XR	420	67 (16%)	
	Placebo	213	15 (7%)	
Triglycerides $\geq$ 200 mg/dL	Schizophrenia <sup>a</sup>	SEROQUEL XR	658	118 (18%)
		Placebo	214	11 (5%)
	Bipolar Depression <sup>b</sup>	SEROQUEL XR	84	7 (8%)
		Placebo	93	7 (8%)
	Bipolar Mania <sup>c</sup>	SEROQUEL XR	102	15 (15%)
		Placebo	125	8 (6%)
Major Depressive Disorder (Adjunct Therapy) <sup>d</sup>	SEROQUEL XR	458	75 (16%)	
	Placebo	223	18 (8%)	
LDL-Cholesterol $\geq$ 160 mg/dL	Schizophrenia <sup>a</sup>	SEROQUEL XR	691	47 (7%)
		Placebo	227	17 (8%)
	Bipolar Depression <sup>b</sup>	SEROQUEL XR	86	3 (4%)
		Placebo	104	2 (2%)
	Bipolar Mania <sup>c</sup>	SEROQUEL XR	125	5 (4%)
		Placebo	135	2 (2%)
Major Depressive Disorder (Adjunct Therapy) <sup>d</sup>	SEROQUEL XR	457	51 (11%)	
	Placebo	219	21 (10%)	
HDL-Cholesterol $\leq$ 40 mg/dL	Schizophrenia <sup>a</sup>	SEROQUEL XR	600	87 (15%)
		Placebo	195	23 (12%)
	Bipolar Depression <sup>b</sup>	SEROQUEL XR	78	7 (9%)
		Placebo	83	6 (7%)
	Bipolar Mania <sup>c</sup>	SEROQUEL XR	100	19 (19%)
		Placebo	115	15 (13%)
Major Depressive Disorder (Adjunct Therapy) <sup>d</sup>	SEROQUEL XR	470	34 (7%)	
	Placebo	230	19 (8%)	

a: 6 weeks duration  
b: 8 weeks duration  
c: 3 weeks duration  
d: 6 weeks duration

In SEROQUEL clinical trials for schizophrenia, the percentage of patients with shifts in cholesterol and triglycerides from baseline to clinically significant levels were 18% (placebo: 7%) and 22% (placebo: 16%). HDL-cholesterol and LDL-cholesterol parameters were not measured in these studies. In SEROQUEL clinical trials for bipolar depression, the following percentage of patients had shifts from baseline to clinically significant levels for the four lipid parameters measured: total cholesterol 9% (placebo: 6%); triglycerides 14% (placebo: 9%); LDL-cholesterol 6% (placebo: 5%) and HDL-cholesterol 14% (placebo: 14%). Lipid parameters were not measured in the bipolar mania studies.

Table 5 shows the percentage of patients in MDD adjunctive therapy trials with clinically significant shifts in total-cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol from normal baseline by dose .

**Table 5: Percentage of Patients with Shifts in Total Cholesterol, Triglycerides, LDL-Cholesterol and HDL-Cholesterol from Normal Baseline to Clinically Significant Levels in MDD Adjunctive Therapy Trials by Dose**

Table 5

<b>Laboratory Analyte</b>	<b>Treatment Arm<sup>a</sup></b>	<b>N</b>	<b>Patients n (%)</b>
Cholesterol $\geq$ 240 mg/dL	Placebo	213	15 (7%)
	SEROQUEL XR 150 mg	223	41 (18%)
	SEROQUEL XR 300 mg	197	26 (13%)
Triglycerides $\geq$ 200 mg/dL	Placebo	223	18 (8%)
	SEROQUEL XR 150 mg	232	36 (16%)
	SEROQUEL XR 300 mg	226	39 (17%)
LDL-Cholesterol $\geq$ 160 mg/dL	Placebo	219	21 (8%)
	SEROQUEL XR 150 mg	242	29 (16%)
	SEROQUEL XR 300 mg	215	22 (17%)

HDL-Cholesterol ≤ 40 mg/dL	Placebo	230	19 (8%)
	SEROQUEL XR 150 mg	238	14 (6%)
	SEROQUEL XR 300 mg	232	20 (9%)

a: 6 weeks duration

**Children and Adolescents:**

Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients, and SEROQUEL XR is not approved for patients under the age of 18 years.

Table 6 shows the percentage of children and adolescents with shifts in total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol from baseline to clinically significant levels by indication in clinical trials with SEROQUEL.

**Table 6: Percentage of Children and Adolescents with Shifts in Total Cholesterol, Triglycerides LDL-Cholesterol and HDL-Cholesterol from Baseline to Clinically Significant Levels by Indication**

**Table 6**

Laboratory Analyte	Indication	Treatment Arm	N	Patients n (%)
Total Cholesterol ≥200 mg/dL	Schizophrenia <sup>a</sup>	SEROQUEL	107	13 (12%)
		Placebo	56	1 (2%)
	Bipolar Mania <sup>b</sup>	SEROQUEL	159	16 (10%)
		Placebo	66	2 (3%)
Triglycerides ≥150 mg/dL	Schizophrenia <sup>a</sup>	SEROQUEL	103	17 (17%)
		Placebo	51	4 (8%)

	Bipolar Mania <sup>b</sup>	SEROQUEL	149	32 (22%)
		Placebo	60	8 (13%)
LDL-Cholesterol $\geq$ 130 mg/dL	Schizophrenia <sup>a</sup>	SEROQUEL	112	4 (4%)
		Placebo	60	1 (2%)
	Bipolar Mania <sup>b</sup>	SEROQUEL	169	13 (8%)
		Placebo	74	4 (5%)
HDL-Cholesterol $\leq$ 40 mg/dL	Schizophrenia <sup>a</sup>	SEROQUEL	104	16 (15%)
		Placebo	54	10 (19%)
	Bipolar Mania <sup>b</sup>	SEROQUEL	154	16 (10%)
		Placebo	61	4 (7%)

a: 13- 17 years, 6 weeks duration

b: 10-17 years, 3 weeks duration

## 5.6 Weight Gain

Increases in weight have been observed in clinical trials. Patients receiving quetiapine should receive regular monitoring of weight [see *Patient Counseling Information (17)*].

**Adults:** Table 7 shows the percentage of adult patients with weight gain of  $\geq 7\%$  of body weight by indication.

**Table 7: Percentage of Patients with Weight Gain  $\geq 7\%$  of Body Weight (Adults) by Indication**

Vital sign	Indication	Treatment Arm	N	Patients n (%)
<b>Weight gain <math>\geq 7\%</math></b>	Schizophrenia <sup>a</sup>	SEROQUEL XR	907	90 (10%)

<b>of body weight</b>		Placebo	299	16 (5%)
	Bipolar Mania <sup>b</sup>	SEROQUEL XR	138	7 (5%)
		Placebo	150	0 (0%)
	Bipolar Depression <sup>c</sup>	SEROQUEL XR	110	9 (8%)
		Placebo	125	1 (1%)
	<u>Major Depressive Disorder (Adjunctive Therapy)</u> <sup>d</sup>	SEROQUEL XR	616	32 (5%)
		Placebo	302	5 (2%)

a: 6 weeks duration

b: 3 weeks duration

c: 8 weeks duration

d: 6 weeks duration

In schizophrenia trials, the proportions of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significant greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%).

Table 8 shows the percentage of adult patients with weight gain of  $\geq 7\%$  of body weight for MDD by dose.

**Table 8: Percentage of Patients with Weight Gain  $\geq 7\%$  of Body Weight in MDD Adjunctive Therapy Trials by Dose (Adults)**

**Table 8**

<b>Vital sign</b>	<b>Treatment Arm</b>	<b>N</b>	<b>Patients n(%)</b>
<b>Weight Gain <math>\geq 7\%</math> of Body in MDD Adjunctive Therapy</b>	Placebo	302	5 (2%)
	SEROQUEL XR 150 mg	309	10 (3%)
	SEROQUEL XR 300 mg	307	22 (7%)

*Children and Adolescents:* Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR

is not approved for patients under the age of 18 years. In two clinical trials with SEROQUEL, one in bipolar mania and one in schizophrenia, reported increases in weight are included in table 9 below

Table 9 shows the percentage of patients with weight gain  $\geq 7\%$  of body weight in clinical trials with SEROQUEL.

**Table 9: Percentage of Patients with Weight Gain  $\geq 7\%$  of Body Weight (Children and Adolescents)**

**Table 9**

Vital sign	Indication	Treatment Arm	N	Patients n (%)
Weight gain	Schizophrenia <sup>a</sup>	SEROQUEL	111	23 (21%)
		Placebo	44	3 (7%)
	Bipolar Mania <sup>b</sup>	SEROQUEL	157	18 (12%)
		Placebo	68	0 (0%)

a: 6 weeks duration

b: 3 weeks duration

The mean change in body weight in the schizophrenia trial was 2.0 kg in the SEROQUEL group and -0.4 kg in the placebo group and in the bipolar mania trial it was 1.7 kg in the SEROQUEL group and 0.4 kg in the placebo group.

In an open-label study that enrolled patients from the above two pediatric trials, 63% of patients (241/380) completed 26 weeks of therapy with SEROQUEL. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Forty-five percent of the patients gained  $\geq 7\%$  of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks, an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on SEROQUEL met this criterion after 26 weeks of treatment.

When treating pediatric patients with SEROQUEL for any indication, weight gain should be assessed against that expected for normal growth.

## 5.7 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs including quetiapine. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL XR should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL XR, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome.

## 5.8 Orthostatic Hypotension

Quetiapine may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its  $\alpha$ 1-adrenergic antagonist properties. Syncope was reported in 0.3% (5/1866) of the patients treated with SEROQUEL XR across all indications, compared

with 0.2% (2/928) on placebo. Syncope was reported in 1% (28/3265) of the patients treated with SEROQUEL, compared with 0.2% (2/954) on placebo. Orthostatic hypotension, dizziness, and syncope may lead to falls.

Quetiapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications) [see Adverse Reactions (6.2)]. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

### **5.9 Increases in Blood Pressure (Children and Adolescents)**

Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In placebo-controlled trials in children and adolescents with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increases at any time in systolic blood pressure ( $\geq 20$  mmHg) was 15.2% (51/335) for SEROQUEL and 5.5% (9/163) for placebo; the incidence of increases at any time in diastolic blood pressure ( $\geq 10$  mmHg) was 40.6% (136/335) for SEROQUEL and 24.5% (40/163) for placebo. In the 26-week open-label clinical trial, one child with a reported history of hypertension experienced a hypertensive crisis. Blood pressure in children and adolescents should be measured at the beginning of, and periodically during treatment.

### **5.10 Leukopenia, Neutropenia and Agranulocytosis**

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to atypical antipsychotic agents, including quetiapine fumarate. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL XR at the first sign of a decline in WBC in absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute

neutrophil count  $<1000/\text{mm}^3$ ) should discontinue SEROQUEL XR and have their WBC followed until recovery [*see Adverse Reactions (6.2)*].

### 5.11 Cataracts

The development of cataracts was observed in association with quetiapine treatment in chronic dog studies [*see Animal Toxicology (13.2)*]. Lens changes have also been observed in adults, children, and adolescents during long-term quetiapine treatment, but a causal relationship to quetiapine use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment.

### 5.12 Seizures

During short-term clinical trials with SEROQUEL XR, seizures occurred in 0.05% (1/1866) of patients treated with SEROQUEL XR across all indications compared to 0.3% (3/928) on placebo. During clinical trials with SEROQUEL, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo. As with other antipsychotics, quetiapine fumarate should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

### 5.13 Hypothyroidism

*Adults:* In SEROQUEL XR clinical trials across all indications 1.8% (24/1336) of patients on SEROQUEL XR vs. 0.6% (3/530) on placebo experienced decreased free thyroxine and 1.6% (21/1346) on SEROQUEL XR vs. 1.9% (18/534) on placebo experienced increased thyroid stimulating hormone (TSH); however, no patients experienced a combination of clinically significant decreased free thyroxine and increased TSH. Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients and levels of thyroid binding globulin (TBG) were unchanged. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.7% (26/3489) of SEROQUEL patients

did experience TSH increases in monotherapy studies. Six of these patients with TSH increases needed replacement thyroid treatment.

*Children and Adolescents:* Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts to potentially clinically important thyroid function values at any time for SEROQUEL treated patients and placebo-treated patients for elevated TSH was 2.9% (8/280) vs. 0.7% (1/138), respectively and for decreased total thyroxine was 2.8% (8/289) vs. 0% (0/145), respectively. Of the SEROQUEL treated patients with elevated TSH levels, 1 had simultaneous low free T4 level at end of treatment.

#### **5.14 Hyperprolactinemia**

*Adults:* During clinical trials with quetiapine across all indications, the incidence of shifts in prolactin levels to a clinically significant value occurred in 3.6% (158/4416) of patients treated with quetiapine compared to 2.6% (51/1968) on placebo.

*Children and Adolescents:* Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with bipolar mania (3-week duration) or schizophrenia (6-week duration), the incidence of shifts in prolactin levels to a clinically significant value (>20 µg/L males; > 26 µg/L females at any time) was 13.4% (18/134) for SEROQUEL compared to 4% (3/75) for placebo in males and 8.7% (9/104) for SEROQUEL compared to 0% (0/39) for placebo in females.

Like other drugs that antagonize dopamine D2 receptors, SEROQUEL XR elevates prolactin levels in some patients and the elevation may persist during chronic administration. Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of

potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in carcinogenicity studies conducted in mice and rats. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive [*see Carcinogenesis, Mutagenesis, Impairment of Fertility* (13.1)].

### **5.15 Transaminase Elevations**

Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in a pool of placebo controlled trials ranged between 1% and 2% for SEROQUEL XR compared to 2% for placebo. In schizophrenia trials in adults, the proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo controlled trials were approximately 6% (29/483) for SEROQUEL compared to 1% (3/194) for placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with quetiapine.

### **5.16 Potential for Cognitive and Motor Impairment**

Somnolence was a commonly reported adverse event reported in patients treated with quetiapine especially during the 3-day period of initial dose titration. In schizophrenia trials, somnolence was reported in 24.7% (235/951) of patients on SEROQUEL XR compared to 10.3% (33/319) of placebo patients. In a bipolar depression clinical trial, somnolence was reported in 51.8% (71/137) of patients on SEROQUEL XR compared to 12.9% (18/140) of placebo patients. In a clinical trial for bipolar mania, somnolence was reported in 50.3% (76/151) of patients on SEROQUEL XR compared to 11.9% (19/160) of placebo patients. Since quetiapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that quetiapine therapy does not affect them adversely. Somnolence may lead to falls.

In short-term adjunctive therapy trials for MDD, somnolence was reported in 40% (252/627) of patients on SEROQUEL XR respectively compared to 9% (27/309) of placebo patients. Somnolence was dose-related in these trials (37% (117/315) and 43% (135/312) for the 150 mg and 300 mg groups, respectively).

### **5.17 Priapism**

One case of priapism in a patient receiving quetiapine was reported prior to market introduction. While a causal relationship to use of quetiapine has not been established, other drugs with  $\alpha$ -adrenergic blocking effects have been reported to induce priapism, and it is possible that quetiapine may share this capacity. Severe priapism may require surgical intervention.

### **5.18 Body Temperature Regulation**

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL XR for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

### **5.19 Dysphagia**

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL XR and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

### **5.20 Suicide**

The possibility of a suicide attempt is inherent in schizophrenia, bipolar disorder and depression; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL XR should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

In three, 6-week clinical studies in patients with schizophrenia (N=951) the incidence of treatment emergent suicidal ideation or suicide attempt was 0.6% (n=6) in SEROQUEL XR treated patients and 0.9% (n=3) in placebo-treated patients.

In an 8-week clinical study in patients with bipolar depression (N=137 for SEROQUEL XR and 140 for placebo) the incidence of treatment emergent suicidal ideation or suicide attempt was 0.7% (n=1) for SEROQUEL XR treated patients and 1.4% (n=2) for placebo.

In a 3-week clinical study in patients with bipolar mania (N=311, 151 for SEROQUEL XR and 160 for placebo) the incidence of treatment

emergent suicidal ideation or suicide attempt was 1.3% (n=2) for SEROQUEL XR compared to 3.8% (n=6) for placebo.

In two, 6-week MDD adjunctive therapy trials (n=936, 627 on SEROQUEL XR and 309 on placebo) the incidence of treatment emergent suicidal ideation or suicide attempt was 0.5% (n=3) in SEROQUEL XR treated patients and 0.6% (n=2) in placebo.

### **5.21 Use in Patients with Concomitant Illness**

Clinical experience with SEROQUEL XR in patients with certain concomitant systemic illnesses [*see Pharmacokinetics (12.3)*] is limited.

SEROQUEL XR has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL XR, caution should be observed in cardiac patients [*see Warnings and Precautions (5.8)*].

### **5.22 Withdrawal**

Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotic drugs, including quetiapine fumarate. Gradual withdrawal is advised.

In short-term placebo-controlled, monotherapy clinical trials, in patients with MDD, which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was 16.0% (89/556) for quetiapine and 7.3% (29/400) for placebo. The incidence of the individual adverse events (ie, insomnia, nausea, headache, diarrhea, vomiting, dizziness and irritability) did not exceed 6.7% in any treatment group and usually resolved after 1 week post-discontinuation.

## **6 ADVERSE REACTIONS**

### **6.1 Clinical Studies Experience**

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The information below is derived from a clinical trial database for SEROQUEL XR consisting of approximately 3400 patients exposed to SEROQUEL XR for the treatment of Schizophrenia, Bipolar Disorder, and Major Depressive Disorder in placebo controlled trials. This

experience corresponds to approximately 1020.1 patient-years. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, body weights, laboratory analyses and ECG results.

Adverse reactions during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized event categories. In the tables and tabulations that follow, standard MedDRA terminology has been used to classify reported adverse reactions.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

#### Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

*Schizophrenia:* There was no difference in the incidence and type of adverse reactions associated with discontinuation (6.4% (61/951) for SEROQUEL XR vs. 7.5% (24/319) for placebo) in a pool of controlled Schizophrenia trials. There were no adverse reactions leading to discontinuation that occurred at an incidence of  $\geq 2\%$  for SEROQUEL XR in Schizophrenia trials.

#### *Bipolar Disorder:*

*Mania:* In a single clinical trial in patients with bipolar mania, 4.6% (7/151) of patients on SEROQUEL XR discontinued due to adverse reaction compared to 8.1% (13/160) on placebo. There were no adverse reactions leading to discontinuation that occurred at an incidence of  $\geq 2\%$  for SEROQUEL XR in Bipolar Mania trials.

*Depression:* In a single clinical trial in patients with bipolar depression, 14% (19/137) of patients on SEROQUEL XR discontinued due to adverse reaction compared to 4% (5/140) on placebo. Somnolence\* was the only adverse reaction leading to discontinuation that occurred at an incidence of  $\geq 2\%$  in SEROQUEL XR in Bipolar Depression trials.

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\* The adverse reaction term “somnolence” includes both “somnolence” and “sedation.”

*MDD, Adjunctive Therapy:* In adjunctive therapy clinical trials in patients with MDD, 12.1% (76/627) of patients on SEROQUEL XR discontinued due to adverse reaction compared to 1.9% (5/309) on placebo. Somnolence\* was the only adverse reaction leading to discontinuation that occurred at an incidence of  $\geq 2\%$  in SEROQUEL XR in MDD trials.

**Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials:**

In short-term placebo-controlled studies for schizophrenia the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were somnolence (25%), dry mouth (12%), dizziness (10%), and dyspepsia (5%).

**Adverse Reactions Occurring at an Incidence of 1% or More Among SEROQUEL XR Treated Patients in Short-Term, Placebo-Controlled Trials**

Table 12 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of schizophrenia (up to 6 weeks) in 1% or more in patients treated with SEROQUEL XR (doses ranging from 300 to 800 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

**Table 12: Treatment-Emergent Adverse Reaction Incidence in 6-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia<sup>1</sup>**

<b>Body System/Preferred Term</b>	<b>Placebo (n=319)</b>	<b>SEROQUEL XR (n=951)</b>
<b>Cardiac Disorders</b>		
Tachycardia	1%	3%
<b>Eye Disorders</b>		

Vision blurred	1%	2%
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#### **Gastrointestinal Disorders**

Dry Mouth	1%	12%
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Constipation	5%	6%
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Dyspepsia	2%	5%
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Toothache	0%	2%
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#### **General Disorders and Administration Site Conditions**

Fatigue	2%	3%
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Irritability	0%	1%
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Pyrexia	0%	1%
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#### **Investigations**

Heart Rate Increased	1%	4%
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#### **Metabolism and Nutrition Disorders**

Increased Appetite	<b>0%</b>	<b>2%</b>
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#### **Musculoskeletal and Connective Tissue Disorders**

Muscle Spasms	1%	2%
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#### **Nervous System Disorders**

Somnolence <sup>2</sup>	10%	25%
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Dizziness	4%	10%
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Tremor	1%	2%
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Akathisia	1%	2%
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Extrapyramidal Symptoms <sup>3</sup>	5%	8%
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#### **Psychiatric Disorders**

Anxiety	1%	2%
Schizophrenia	1%	2%
Restlessness	1%	2%
<b>Vascular Disorders</b>		
Orthostatic Hypotension	5%	7%
Hypotension	1%	3%

<sup>1</sup>Reactions for which the SEROQUEL XR incidence was 1% or more and equal to or less than placebo are not listed in the table, but included the following: headache, insomnia, and nausea, vomiting, diarrhea, stomach discomfort, weight increased, diastolic blood pressure decreased, systolic blood pressure decreased, arthralgia, back pain, pain in extremity, extrapyramidal disorder, agitation, psychotic disorder, sleep disorder, nasal congestion, hypertension.

<sup>2</sup>Somnolence combines adverse reaction terms somnolence and sedation.

<sup>3</sup>Extrapyramidal symptoms that were reported for SEROQUEL XR or placebo include the terms: akathisia, cogwheel rigidity, drooling, dyskinesia dystonia, extrapyramidal disorder, hypertonica, movement disorder, muscle rigidity, oculogyration, parkinsonism, parkinsonian gait, psychomotor hyperactivity, tardive dyskinesia, restlessness and tremor.

In a 3-week, placebo controlled study in bipolar mania the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were somnolence (50%), dry mouth (34%), dizziness (10%), constipation (10%), weight gain (7%), dysarthria (5%), and nasal congestion (5%).

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of bipolar mania (up to 3 weeks) in 1% or more of patients treated with SEROQUEL XR (doses ranging from 400 to 800 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

**Table 13: Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial for the Treatment of Bipolar Mania<sup>1</sup>**

**Table 13**

<b>Body System/Preferred Term</b>	<b>Placebo (n=160)</b>	<b>SEROQUEL XR (n=151)</b>
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**Cardiac Disorders**

Tachycardia	1%	2%
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**Eye Disorders**

Vision blurred	1%	2%
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**Gastrointestinal Disorders**

Dry Mouth	7%	34%
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Constipation	3%	10%
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Dyspepsia	4%	7%
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Toothache	1%	3%
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**General Disorders and Administration Site Conditions**

Fatigue	4%	7%
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Sluggishness	1%	2%
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Pain	0%	1%
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**Investigations**

Weight Gain	1%	7%
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Heart Rate Increased	0%	3%
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**Injury, Poisoning And Procedural Complications**

Contusion	0%	1%
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**Metabolism And Nutrition Disorders**

Increased Appetite	2%	4%
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**Nervous System Disorders**

Extrapyramidal Symptoms <sup>3</sup>	4%	7%
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Somnolence <sup>2</sup>	12%	50%
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Dizziness	4%	10%
Dysarthria	0%	5%
Lethargy	1%	2%
Postural Dizziness	0%	1%

**Musculoskeletal And Connective Tissue Disorders**

Back Pain	2%	3%
Arthralgia	0%	1%

**Psychiatric Disorders**

Abnormal Dreams	0%	3%
Bipolar I Disorder	0%	1%

**Respiratory, Thoracic and Mediastinal Disorders**

Nasal Congestion	1%	5%
Dry Throat	0%	1%

**Vascular Disorders**

Orthostatic Hypotension	0%	3%
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<sup>1</sup>Reactions for which the SEROQUEL XR incidence was 1% or more and equal to or less than placebo are not listed in the table, but included the following: headache, peripheral edema, diarrhea, nausea, vomiting, decreased appetite, muscle spasms, musculoskeletal stiffness, myalgia, tremor, akathisia, insomnia, agitation, nightmare, restlessness, erectile dysfunction, pharyngolaryngeal pain, cough, and hypotension. <sup>2</sup>Somnolence combines adverse reaction terms somnolence and sedation.

<sup>3</sup>Extrapyramidal symptoms that were reported for SEROQUEL XR or placebo include the terms: akathisia, cogwheel rigidity, dystonia, extrapyramidal disorder, restlessness and tremor.

In the 8-week placebo-controlled bipolar depression study, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were somnolence (52%), dry mouth (37%), increased appetite (12%), weight gain (7%), dyspepsia (7%), and fatigue (6%).

Table 14: enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute

therapy of bipolar depression (up to 8 weeks) in 1% or more of patients treated with SEROQUEL XR 300 mg/day where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

**Table 14: Treatment-Emergent Adverse Reactions in an 8-Week Placebo-Controlled Clinical Trial for the Treatment of Bipolar Depression<sup>1</sup>**

<b>Body System/Preferred Term</b>	<b>Placebo (n=140)</b>	<b>SEROQUEL XR (n=137)</b>
<b>Ear And Labyrinth Disorders</b>		
Ear Pain	1%	2%
<b>Gastrointestinal Disorders</b>		
Dry Mouth	7%	37%
Constipation	6%	8%
Dyspepsia	1%	7%
Toothache	0%	3%
Abdominal Distension	0%	
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	2%	6%
Irritability	3%	4%
<b>Immune System Disorders</b>		
Seasonal Allergy	1%	2%
<b>Infections And Infestations</b>		
Viral Gastroenteritis	1%	4%

Urinary Tract Infection	0%	2%
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Sinusitis	1%	2%
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### **Investigations**

Weight Gain	1%	7%
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Heart Rate Increased	0%	2%
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### **Metabolism and Nutrition Disorder**

Increased Appetite	6%	12%
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Decreased Appetite	1%	2%
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### **Musculoskeletal And Connective Tissue Disorders**

Arthralgia	1	4
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Back Pain	1%	3%
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Muscle Spasms	1%	3%
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Myalgia	1%	2%
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Neck Pain	0%	2%
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### **Nervous System Disorders**

Somnolence <sup>2</sup>	13%	52%
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Extrapyramidal Symptoms <sup>3</sup>	1%	4%
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Dizziness	11%	13%
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Paraesthesia	2%	3%
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Disturbance in Attention	1%	2%
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Dysarthria	0%	2%
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Akathisia	0%	2%
Hypersomnia	0%	2%
Mental Impairment	0%	2%
Migraine	1%	2%
Restless Legs Syndrome	1%	2%
Sinus Headache	1%	2%

### **Psychiatric Disorders**

Abnormal Dreams	0%	3%
Anxiety	1%	2%
Confusional State	0%	2%
Disorientation	0%	2%
Libido Decreased	1%	2%

### **Renal And Urinary Disorders**

Pollakiuria	1%	2%
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### **Respiratory, Thoracic And Mediastinal Disorders**

Sinus Congestion	1%	2%
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### **Skin And Subcutaneous Tissue Disorders**

Hyperhidrosis	1%	2%
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### **Vascular Disorders**

Orthostatic Hypotension	1%	2%
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<sup>1</sup>Reactions for which the SEROQUEL XR incidence was 1% or more and equal to or less than placebo are not listed in the table, but included the following: headache insomnia, nausea, diarrhea, vomiting, nasopharyngitis, upper respiratory tract infection, influenza, pain in extremity, cough and nasal congestion.

<sup>2</sup>Somnolence combines adverse reaction terms somnolence and sedation.

<sup>3</sup>Extrapyramidal symptoms that were reported for SEROQUEL XR or placebo include the terms: akathisia, dystonia, extrapyramidal disorder, hypertonia, and tremor.

In the 6-week placebo-controlled fixed dose adjunctive therapy clinical trials, for MDD, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater and observed at a rate on SEROQUEL XR and at least twice that of placebo) were somnolence (150 mg: 37%; 300 mg: 43%), dry mouth (150 mg: 27%; 300 mg: 40%), fatigue (150 mg: 14%; 300 mg: 11%) and constipation (150 mg only: 11%).

Table 15 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during short-term adjunctive therapy of MDD (up to 6 weeks) in 1% or more of patients treated with SEROQUEL XR (at doses of either 150 mg or 300 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

**Table 15: Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Adjunctive Therapy Clinical Trials for the Treatment of MDD by Fixed Dose<sup>1</sup>**

<b>Body System/Preferred Term</b>	<b>Placebo (n=309)</b>	<b>SEROQUEL XR 150 mg(n=315)</b>	<b>SEROQUEL XR 300 mg (n=312)</b>
<b>Ear And Labyrinth Disorders</b>			
Vertigo	1%	2%	2%
<b>Eye Disorders</b>			
Vision Blurred	1%	2%	1%
<b>Gastrointestinal Disorders</b>			
Dry Mouth	8%	27%	40%
Constipation	4%	6%	11%
Nausea	7%	7%	8%
Dyspepsia	2%	2%	3%
Abdominal Distension	0%	0%	1%
Vomiting	1%	3%	1%

**General Disorders and Administration Site Conditions**

Fatigue	4%	14%	11%
Irritability	3%	4%	2%
Chills	0%	1%	1%

**Infections And Infestations**

Upper Respiratory Tract Infection	2%	3%	2%
Influenza	0%	2%	1%

**Injury, Poisoning And Procedural Complications**

Fall	1%	2%	0%
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**Investigations**

Weight Increased	0%	3%	5%
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**Metabolism And Nutrition Disorders**

Increased Appetite	3%	3%	5%
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**Musculoskeletal And Connective Tissue Disorders**

Back pain	1%	3%	3%
Muscle Spasms	1%	2%	1%

**Nervous System Disorders**

Somnolence <sup>2</sup>	9%	37%	43%
Dizziness	7%	11%	12%
Extrapyramidal Symptoms <sup>3</sup>	4%	4%	6%
Hypersomnia	0%	1%	2%

Dysarthria	0%	1%	1%
Dysgeusia	0%	1%	1%
Lethargy	1%	2%	1%
Akathisia	1%	2%	2%

#### Psychiatric Disorders

Abnormal Dreams	1%	2%	2%
Anxiety	1%	2%	2%
Restlessness	1%	1%	2%
Libido Decreased	0%	0%	1%
Depression	1%	2%	1%

<sup>1</sup>Reactions for which the SEROQUEL XR incidence was 1% or more but equal to or less than placebo are not listed in the table, but included the following: headache, insomnia, nausea, disturbance in attention, dysarthria, paraesthesia, tremor, diarrhea, upper abdominal pain, nightmare, nasopharyngitis, sinusitis, decreased appetite, myalgia, arthralgia, pain in extremity, hyperhidrosis, night sweats and nasal congestion.

<sup>2</sup>Somnolence combines adverse event terms somnolence and sedation.

<sup>3</sup>Extrapyramidal symptoms that were reported for SEROQUEL XR or placebo include the terms: akathisia, cogwheel rigidity, drooling, dyskinesia, extrapyramidal disorder, hypertonia, hypokinesia, psychomotor hyperactivity, restlessness, and tremor.

#### Adverse Reactions Occurring at an Incidence of 5% or More Among SEROQUEL XR Treated Patients in Long-Term, Placebo-Controlled Trials

In a longer-term placebo-controlled trial, adult patients with schizophrenia who remained clinically stable on SEROQUEL XR during open-label treatment for at least 4 months were randomized to placebo (n=103) or to continue on their current SEROQUEL XR (n=94) for up to 12 months of observation for possible relapse, the adverse reactions reported were generally consistent with those reported in the short-term, placebo-controlled trials. Insomnia (8.5%) and headache (7.4%) were the only adverse events reported by 5% or more patients.

Adverse Reactions that occurred in <5% of patients and were considered drug-related (incidence greater than placebo and consistent with known pharmacology of drug class) in order of decreasing frequency:

heart rate increased, hypotension, weight increased, tremor, akathisia, increased appetite, blurred vision, postural dizziness, pyrexia, dysarthria, dystonia, drooling, syncope, tardive dyskinesia, dysphagia, leukopenia, and rash.

Adverse Reactions in clinical trials with quetiapine and not listed elsewhere in the label:

nightmares, peripheral edema, rhinitis, eosinophilia, hypersensitivity, elevations in gamma-GT levels, and elevations in serum creatine phosphokinase (not associated with NMS).

#### Extrapyramidal Symptoms (EPS):

##### **Dystonia**

*Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Four methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) Barnes Akathisia Rating Scale (BARS) Global Assessment Score, (3) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (4) use of anticholinergic medications to treat emergent EPS.

*Adults:* In placebo-controlled clinical trials with quetiapine, utilizing doses up to 800 mg per day, the incidence of any adverse reactions potentially related to EPS ranged from 8% to 11% for quetiapine and 4% to 11% for placebo.

In three-arm placebo-controlled clinical trials for the treatment of schizophrenia, utilizing doses between 300 mg and 800 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 8% for SEROQUEL XR and 8% for SEROQUEL

(without evidence of being dose related), and 5% in the placebo group. In these studies, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, and muscle rigidity) was generally low and did not exceed 3% for any treatment group.

At the end of treatment, the mean change from baseline in SAS total score and BARS Global Assessment score was similar across the treatment groups. The use of concomitant anticholinergic medications was infrequent and similar across the treatment groups. The incidence of extrapyramidal symptoms was consistent with that seen with the profile of SEROQUEL in schizophrenia patients.

**Table 16: Adverse Experiences Associated with Extrapyramidal Symptoms in Placebo-controlled Clinical Trials for Schizophrenia**

Preferred term	Placebo (N=319)		SEROQUEL XR 300 mg/day (N=91)		SEROQUEL XR 400 mg/day (N=227)		SEROQUEL XR 600 mg/day (N=310)		SEROQUEL XR 800 mg/day (N=323)		All Doses (N=951)	
	n	%	n	%	n	%	n	%	n	%	n	%
Dystonic event <sup>a</sup>	0	0.0	3	3.3	0	0.0	4	1.3	1	0.3	8	0.8
Parkinsonism <sup>b</sup>	4	1.3	1	1.1	3	1.3	11	3.6	7	2.2	22	2.3
Akathisia <sup>c</sup>	4	1.3	0	0.0	3	1.3	7	2.3	7	2.2	17	1.8
Dyskinetic event <sup>d</sup>	2	0.6	2	2.2	1	0.4	1	0.3	1	0.3	5	0.5
Other extrapyramidal event <sup>e</sup>	7	2.2	3	3.3	4	1.8	7	2.3	12	3.7	26	2.7

- a: Patients with the following terms were counted in this category: nuchal rigidity, hypertonia, dystonia, muscle rigidity, oculogyration
- b: Patients with the following terms were counted in this category: cogwheel rigidity, tremor, drooling, hypokinesia
- c: Patients with the following terms were counted in this category: akathisia, psychomotor agitation
- d: Patients with the following terms were counted in this category: tardive dyskinesia, dyskinesia, choreoathetosis
- e: Patients with the following terms were counted in this category: restlessness; extrapyramidal disorder, movement disorder

In a placebo-controlled clinical trial for the treatment of bipolar mania, utilizing the dose range of 400-800 mg/day of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 6.6% for SEROQUEL XR and 3.8% in the placebo group. In this study, the incidence of the individual adverse reactions (eg, akathisia,

extrapyramidal disorder, tremor, dystonia, restlessness, and cogwheel rigidity) did not exceed 2.0% for any adverse reaction.

**Table 17: Adverse Experiences Associated with Extrapyramidal Symptoms in a Placebo-controlled Clinical Trial for Bipolar Mania**

Preferred term*	Placebo (N=160)		SEROQUEL XR (N=151)	
	n	%	n	%
Dystonic event <sup>a</sup>	0	0.0	1	0.7
Parkinsonism <sup>b</sup>	3	1.9	4	2.7
Akathisia <sup>c</sup>	1	0.6	2	1.3
Other extrapyramidal event <sup>d</sup>	2	1.3	3	2.0

\*: There were no adverse experiences with the preferred term of dyskinetic event.

a: Patients with the following terms were counted in this category: nuchal rigidity, hypertonia, dystonia, muscle rigidity, oculogyration

b: Patients with the following terms were counted in this category: cogwheel rigidity, tremor, drooling, hypokinesia

c: Patients with the following terms were counted in this category: akathisia, psychomotor agitation

d: Patients with the following terms were counted in this category: restlessness; extrapyramidal disorder, movement disorder

In a placebo-controlled clinical trial for the treatment of bipolar depression utilizing 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 4.4% for SEROQUEL XR and 0.7% in the placebo group. In this study, the incidence of the individual adverse reactions (eg. akathisia, extrapyramidal disorder, tremor, dystonia, hypertonia) did not exceed 1.5% for any individual adverse reaction.

**Table 18: Adverse Experiences Associated with Extrapyramidal Symptoms in a Placebo-controlled Clinical Trial for Bipolar Depression**

Preferred term*	Placebo (N=140)		SEROQUEL XR (N=137)	
	n	%	n	%

Dystonic event <sup>a</sup>	0	0.0	2	1.5
Parkinsonism <sup>b</sup>	1	0.7	1	0.7
Akathisia <sup>c</sup>	0	0.0	2	1.5
Other extrapyramidal event	0	0.0	1	0.7

\*: There were no adverse experiences with the preferred term of dyskinesic event.

a: Patients with the following terms were counted in this category: nuchal rigidity, hypertonia, dystonia, muscle rigidity, oculogyration

b: Patients with the following terms were counted in this category: cogwheel rigidity, tremor, drooling, hypokinesia

c: Patients with the following terms were counted in this category: akathisia, psychomotor agitation

d: Patients with the following terms were counted in this category: restlessness; extrapyramidal disorder, movement disorder

In two placebo-controlled short-term adjunctive therapy clinical trials for the treatment of MDD utilizing between 150 mg and 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 5.1% SEROQUEL XR and 4.2% for the placebo group.

Table 19 shows the percentage of patients experiencing adverse reactions potentially associated with EPS in adjunct clinical trials for MDD by dose:

**Table 19: Adverse Reactions Potentially Associated with EPS in MDD Trials by Dose, Adjunctive Therapy Clinical Trials (6 weeks duration)**

Preferred term	Placebo (N=309)		SEROQUEL XR 150 mg/day (N=315)		SEROQUEL XR 300 mg/day (N=312)		All Doses (N=627)	
	n	%	n	%	n	%	n	%
Dystonic event <sup>a</sup>	0	0.0	1	0.3	0	0.0	1	0.2
Parkinsonism <sup>b</sup>	5	1.6	3	1.0	4	1.3	7	1.1
Akathisia <sup>c</sup>	3	1.0	5	1.6	8	2.6	12	2.1
Dyskinetic event <sup>d</sup>	0	0.0	0	0.0	1	0.3	1	0.2

Other extrapyramidal event <sup>e</sup>	5	1.6	5	1.6	7	2.2	12	1.9f
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- a: Patients with the following terms were counted in this category: nuchal rigidity, hypertonia, dystonia, muscle rigidity, oculogyration
- b: Patients with the following terms were counted in this category: cogwheel rigidity, tremor, drooling, hypokinesia
- c: Patients with the following terms were counted in this category: akathisia, psychomotor agitation
- d: Patients with the following terms were counted in this category: tardive dyskinesia, dyskinesia, choreoathetosis
- e: Patients with the following terms were counted in this category: restlessness; extrapyramidal disorder, movement disorder

*Children and Adolescents:* Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In a short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration), the aggregated incidence of extrapyramidal symptoms was 12.9% for SEROQUEL and 5.3% for placebo, though the incidence of the individual adverse events (eg, akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration), the aggregated incidence of extrapyramidal symptoms was 3.6% for SEROQUEL and 1.1% for placebo.

Table 20 below presents a listing of patients with AEs potentially associated with EPS in the short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration).

**Table 20: Adverse experiences potentially associated with EPS in the short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration).**

Preferred term	Placebo (N=75)		Quetiapine 400 mg/day (N=73)		Quetiapine 800 mg/day (N=74)		All Quetiapine (N=147)	
	n	%	n	%	n	%	n	%
Dystonic event <sup>a</sup>	0	0.0	2	2.7	0	0.0	2	1.4
Parkinsonism <sup>b</sup>	2	2.7	4	5.5	4	5.4	8	5.4
Akathisia <sup>c</sup>	3	4.0	3	4.1	4	5.4	7	4.8
Dyskinetic event <sup>d</sup>	0	0.0	2	2.7	0	0.0	2	1.4
Other extrapyramidal event <sup>e</sup>	0	0.0	2	2.7	2	2.7	4	2.7

a: Patients with the following terms were counted in this category: nuchal rigidity, hypertonia, dystonia, muscle rigidity

b: Patients with the following terms were counted in this category: cogwheel rigidity, tremor

c: Patients with the following terms were counted in this category: akathisia

d: Patients with the following terms were counted in this category: tardive dyskinesia, dyskinesia, choreoathetosis

e: Patients with the following terms were counted in this category: restlessness; extrapyramidal disorder

Table 21 below presents a listing of patients with Adverse Experiences potentially associated with EPS in a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration)

**Table 21: Adverse experiences potentially associated with EPS in a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration)**

Preferred term*	Placebo (N=90)		Quetiapine 400 mg (N=95)		Quetiapine 600 mg (N=98)		All Quetiapine (N=193)	
	n	%	n	%	n	%	n	%
Parkinsonism <sup>a</sup>	1	1.1	2	2.1	1	1.0	3	1.6
Akathisia <sup>b</sup>	0	0.0	1	1.0	1	1.0	2	1.0
Other extrapyramidal event <sup>c</sup>	0	0.0	1	1.1	1	1.0	2	1.0

- \*: There were no adverse experiences with the preferred term of dystonic or dyskinesic events.
- a: Patients with the following terms were counted in this category: cogwheel rigidity, tremor
- b: Patients with the following terms were counted in this category: akathisia
- c: Patients with the following terms were counted in this category: restlessness; extrapyramidal disorder

*Children and Adolescents:* Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increased appetite was 7.6% for SEROQUEL compared to 2.4% for placebo. In a 26-week open-label study that enrolled patients from the above two pediatric trials, the incidence of increased appetite was 10% for SEROQUEL.

## 6.2 Vital Signs and Laboratory Values

Hyperglycemia, hyperlipidemia, weight gain and orthostatic hypotension have been reported with quetiapine. Increases in blood pressure have also been reported with quetiapine in children and adolescents [*see Warnings and Precautions* (5.4, 5.5, 5.6, 5.8 and 5.9)].

### Laboratory Changes:

#### Neutrophil Counts

In three-arm SEROQUEL XR placebo-controlled monotherapy clinical trials, among patients with a baseline neutrophil count  $\geq 1.5 \times 10^9/L$ , the incidence of at least one occurrence of neutrophil count  $<1.5 \times 10^9/L$  was 1.5% in patients treated with SEROQUEL XR and 1.5% for SEROQUEL, compared to 0.8% in placebo-treated patients.

In placebo-controlled monotherapy clinical trials involving 3368 patients on quetiapine fumarate and 1515 on placebo, the incidence of at least one occurrence of neutrophil count  $<1.0 \times 10^9/L$  among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with quetiapine, compared to 0.1% (2/1349) in patients treated with placebo. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL XR at the first sign of a decline in WBC in absence of other causative factors [*see Warnings and Precautions* (5.9)].

### ECG Changes:

2.5% of SEROQUEL XR patients, and 2.3% of placebo patients, had tachycardia (>120 bpm) at any time during the trials. SEROQUEL XR was associated with a mean increase in heart rate, assessed by ECG, of 6.3 beats per minute compared to a mean increase of 0.5 beats per minute for placebo. This is consistent with the rates for SEROQUEL. The incidence of adverse reactions of tachycardia was 1.9% for SEROQUEL XR compared to 0.5% for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. The slight tendency for tachycardia may be related to quetiapine's potential for inducing orthostatic changes [*see Warnings and Precautions* (5.8)].

*Children and Adolescents:* Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients. In the acute (6-week) schizophrenia trial in adolescents, potentially clinically significant increases in heart rate (> 110 bpm) occurred in 5.2% of patients receiving SEROQUEL 400 mg and 8.5% of patients receiving SEROQUEL 800 mg compared to 0% of patients receiving placebo. Mean increases in heart rate were 3.8 bpm and 11.2 bpm for SEROQUEL 400 mg and 800 mg groups, respectively, compared to a decrease of 3.3 bpm in the placebo group [*see Warnings and Precautions* (5.8)].

In the acute (3-week) bipolar mania trial in children and adolescents, potentially clinically significant increases in heart rate (> 110 bpm) occurred in 1.1% of patients receiving SEROQUEL 400 mg and 2.4% of patients receiving SEROQUEL 600 mg compared to 0% of patients receiving placebo. Mean increases in heart rate were 12.8 bpm and 13.4 bpm for SEROQUEL 400 mg and 600 mg groups, respectively, compared to a decrease of 1.7 bpm in the placebo group [*see Warnings and Precautions* (5.8)].

### 6.3 Post Marketing Experience

The following adverse reactions were identified during post approval use of SEROQUEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction which were temporally related to SEROQUEL therapy includes anaphylactic reaction and galactorrhea.

Other adverse reactions reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomyopathy hyponatremia, myocarditis rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Stevens-Johnson syndrome (SJS), and decreased platelets.

In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been reported.

## **7 DRUG INTERACTIONS**

The risks of using SEROQUEL XR in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL XR, caution should be used when it is taken in combination with other centrally acting drugs. Quetiapine potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be limited while taking quetiapine.

Because of its potential for inducing hypotension, SEROQUEL XR may enhance the effects of certain antihypertensive agents.

SEROQUEL XR may antagonize the effects of levodopa and dopamine agonists.

### **7.1 The Effect of Other Drugs on Quetiapine**

#### **Phenytoin**

Coadministration of quetiapine (250 mg three times/day) and phenytoin (100 mg three times/day) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL XR may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (eg, carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (eg, valproate) [*see Dosage and Administration (2)*].

#### **Divalproex**

Coadministration of quetiapine (150 mg bid) and divalproex (500 mg twice daily) increased the mean maximum plasma concentration of quetiapine at steady-state by 17% without affecting the extent of absorption or mean oral clearance.

#### **Thioridazine**

Thioridazine (200 mg twice daily) increased the oral clearance of quetiapine (300 mg twice daily) by 65%.

### Cimetidine

Administration of multiple daily doses of cimetidine (400 mg three times daily for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg three times daily). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

### P450 3A Inhibitors

Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution (reduced dosage) is indicated when SEROQUEL XR is administered with ketoconazole and other inhibitors of cytochrome P450 3A (eg, itraconazole, fluconazole, erythromycin, protease inhibitors).

### Fluoxetine, Imipramine, Haloperidol, and Risperidone

Coadministration of fluoxetine (60 mg once daily), imipramine (75 mg twice daily), haloperidol (7.5 mg twice daily), or risperidone (3 mg twice daily) with quetiapine (300 mg twice daily) did not alter the steady-state pharmacokinetics of quetiapine.

## **7.2. Effect of Quetiapine on Other Drugs**

### Lorazepam

The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg three times daily dosing.

### Divalproex

The mean maximum concentration and extent of absorption of total and free valproic acid at steady-state were decreased by 10 to 12% when divalproex (500 mg twice daily) was administered with quetiapine (150 mg twice daily). The mean oral clearance of total valproic acid (administered as divalproex 500 mg twice daily) was increased by 11% in the presence of quetiapine (150 mg twice daily). The changes were not significant.

### Lithium

Concomitant administration of quetiapine (250 mg three times daily) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

### Antipyrine

Administration of multiple daily doses up to 750 mg/day (on a three times daily schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate

that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C:

There are no adequate and well-controlled studies of SEROQUEL XR use in pregnant women. In limited published literature, there were no major malformations associated with quetiapine exposure during pregnancy. In animal studies, embryo-fetal toxicity occurred. Quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are limited published data on the use of quetiapine for treatment of schizophrenia and other psychiatric disorders during pregnancy. In a prospective observational study, 21 women exposed to quetiapine and other psychoactive medications during pregnancy delivered infants with no major malformations. Among 42 other infants born to pregnant women who used quetiapine during pregnancy, there were no major malformations reported (one study of 36 women, 6 case reports). Due to the limited number of exposed pregnancies, these postmarketing data do not reliably estimate the frequency or absence of adverse outcomes.

When pregnant rats and rabbits were exposed to quetiapine during organogenesis, there was no increase in the incidence of major malformations in fetuses at doses up to 2.4 times the maximum recommended human dose for schizophrenia (MRHD, 800 mg/day on a mg/m<sup>2</sup> basis); however, there was evidence of embryo-fetal toxicity. In rats, delays in skeletal ossification occurred at 0.6 and 2.4 times the MRHD and in rabbits at 1.2 and 2.4 times the MRHD. At 2.4 times the MRHD, there was an increased incidence of carpal/tarsal flexure (minor soft tissue anomaly) in rabbit fetuses and decreased fetal weights in both species. Maternal toxicity (decreased body weights and/or death) occurred at 2.4 times the MRHD in rats and at 0.6-2.4 times the MRHD (all doses) in rabbits.

In a peri/postnatal reproductive study in rats, no drug-related effects were observed when pregnant dams were treated with quetiapine at doses 0.01, 0.12, and 0.24 times the MRHD. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 3.0 times the MRHD.

### **8.2 Labor and Delivery**

The effect of SEROQUEL XR on labor and delivery in humans is unknown.

### **8.3 Nursing Mothers**

SEROQUEL XR was excreted into human milk. Caution should be exercised when SEROQUEL XR is administered to a nursing woman.

In published case reports, the level of quetiapine in breast milk ranged from undetectable to 170 µg/L. The estimated infant dose ranged from 0.09% to 0.43% of the weight-adjusted maternal dose. Based on a limited number (N=8) of mother/infant pairs, calculated infant daily doses range from less than 0.01 mg/kg (at a maternal daily dose up to 100 mg quetiapine) to 0.1 mg/kg (at a maternal daily dose of 400 mg).

### **8.4 Pediatric Use**

Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years [*see Warnings and Precautions (5) and Adverse Reactions (6)*].

In general, the adverse reactions observed in children and adolescents during the clinical trials with SEROQUEL were similar to those in the adult population with few exceptions. Increases in systolic and diastolic blood pressure occurred in children and adolescents and did not occur in adults. Orthostatic hypotension occurred more frequently in adults (4-7%) compared to children and adolescents (< 1%).

### **8.5 Geriatric Use**

Sixty-eight patients in clinical studies with SEROQUEL XR were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL XR in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL XR, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients [*see Dosage and Administration (2.3) and Pharmacokinetics (12.3)*].

### **8.6 Renal Impairment**

Clinical experience with SEROQUEL XR in patients with renal impairment [*see Clinical Pharmacology (12.3)*] is limited.

### **8.7 Hepatic Impairment**

Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage

adjustment may be needed [see *Dosage and Administration* (2.3) and *Clinical Pharmacology* (12.3)].

## **9 DRUG ABUSE AND DEPENDENCE**

### **9.1 Controlled Substance**

SEROQUEL XR is not a controlled substance.

### **9.2 Abuse**

SEROQUEL XR has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL XR (eg, development of tolerance, increases in dose, drug-seeking behavior).

## **10 OVERDOSAGE**

### **10.1 Human Experience**

In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose [see *Warnings and Precautions* (5.4)]. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation.

### **10.2 Management of Overdosage**

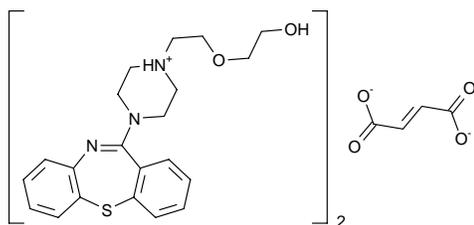
In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-

prolonging effects when administered in patients with acute overdose of SEROQUEL XR. Similarly it is reasonable to expect that the  $\alpha$ -adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL XR. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since  $\beta$  stimulation may worsen hypotension in the setting of quetiapine-induced  $\alpha$  blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

## 11 DESCRIPTION

SEROQUEL XR (quetiapine fumarate) is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo [*b,f*] [1,4]thiazepin-11-yl-1-piperazinyloxy)-ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is  $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$  and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL XR is supplied for oral administration as 50 mg (peach), 150 mg (white), 200 mg (yellow), 300 mg (pale yellow), and 400 mg (white). All tablets are capsule shaped and film coated.

Inactive ingredients for SEROQUEL XR are lactose monohydrate, microcrystalline cellulose, sodium citrate, hypromellose, and magnesium stearate. The film coating for all SEROQUEL XR tablets contain hypromellose, polyethylene glycol 400 and titanium dioxide. In addition yellow iron oxide (50, 200 and 300 mg tablets) and red iron oxide (50 tablets) are included in the film coating of specific strengths.

Each 50 mg tablet contains 58 mg of quetiapine fumarate equivalent to 50 mg quetiapine. Each 150 mg tablet contains 173 mg of quetiapine fumarate equivalent to 150 mg quetiapine. Each 200 mg tablet contains 230 mg of quetiapine fumarate equivalent to 200 mg quetiapine. Each 300 mg tablet contains 345 mg of quetiapine fumarate equivalent to 300 mg quetiapine. Each 400 mg tablet contains 461 mg of quetiapine fumarate equivalent to 400 mg quetiapine.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of SEROQUEL XR, as with other drugs having efficacy in the treatment of schizophrenia, bipolar disorder and major depressive disorder (MDD), is unknown. However, it has been proposed that the efficacy of SEROQUEL XR in schizophrenia is mediated through a combination of dopamine type 2 (D2) and serotonin type 2A (5HT2A) antagonism. The active metabolite, N-desalkyl quetiapine (norquetiapine), has similar activity at D2, but greater activity at 5HT2A receptors, than the parent drug (quetiapine). Quetiapine's efficacy in bipolar depression and MDD may partly be explained by the high affinity and potent inhibitory effects that norquetiapine exhibits for the norepinephrine transporter.

Antagonism at receptors other than dopamine and serotonin with similar or greater affinities may explain some of the other effects of quetiapine and norquetiapine: antagonism at histamine H<sub>1</sub> receptors may explain the somnolence, antagonism at adrenergic α<sub>1b</sub> receptors may explain the orthostatic hypotension, and antagonism at muscarinic M<sub>1</sub> receptors may explain the anticholinergic effects.

### 12.2 Pharmacodynamics

Quetiapine and norquetiapine have affinity for multiple neurotransmitter receptors including dopamine D<sub>1</sub> and D<sub>2</sub>, serotonin 5HT<sub>1A</sub> and 5HT<sub>2A</sub>, histamine H<sub>1</sub>, muscarinic M<sub>1</sub>, and adrenergic α<sub>1b</sub> and α<sub>2</sub> receptors. Quetiapine differs from norquetiapine in having no appreciable affinity for muscarinic M<sub>1</sub> receptors whereas norquetiapine has high affinity. Quetiapine and norquetiapine lack appreciable affinity for benzodiazepine receptors.

#### Receptor Affinities (K<sub>i</sub>, nM) for Quetiapine and Norquetiapine

Receptor	Quetiapine	Norquetiapine
Dopamine D <sub>1</sub>	428	99.8
Dopamine D <sub>2</sub>	626	489

Serotonin 5HT <sub>1A</sub>	1040	191
Serotonin 5HT <sub>2A</sub>	38	2.9
Norepinephrine transporter	>10000	34.8
Histamine H <sub>1</sub>	4.41	1.15
Adrenergic $\alpha_1$ b	14.6	46.4
Adrenergic $\alpha_2$	617	1290
Muscarinic M <sub>1</sub>	1086	38.3
Benzodiazepine	>10000	>10000

### 12.3 Pharmacokinetics

Following multiple dosing of quetiapine up to a total daily dose of 800 mg, administered in divided doses, the plasma concentration of quetiapine and norquetiapine, the major active metabolite of quetiapine, were proportional to the total daily dose. Accumulation is predictable upon multiple dosing. Steady-state mean  $C_{max}$  and AUC of norquetiapine are about 21-27% and 46-56%, respectively of that observed for quetiapine. Elimination of quetiapine is mainly via hepatic metabolism. The mean-terminal half-life is approximately 7 hours for quetiapine and approximately 12 hours for norquetiapine within the clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. SEROQUEL XR is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

#### Absorption

Quetiapine fumarate reaches peak plasma concentrations approximately 6 hours following administration. SEROQUEL XR dosed once daily at steady-state has comparable bioavailability to an equivalent total daily dose of SEROQUEL administered in divided doses, twice daily. A high-fat meal (approximately 800 to 1000 calories) was found to produce statistically significant increases in the SEROQUEL XR  $C_{max}$  and AUC of 44% to 52% and 20% to 22%, respectively, for the 50 mg and 300 mg tablets. In comparison, a light meal (approximately 300 calories) had no significant effect on the  $C_{max}$  or AUC of quetiapine. It is recommended that SEROQUEL XR be taken without food or with a light meal [*see Dosage and Administration (2)*].

### Distribution

Quetiapine is widely distributed throughout the body with an apparent volume of distribution of  $10\pm 4$  L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

### Metabolism and Elimination

Following a single oral dose of  $^{14}\text{C}$ -quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively. The average dose fraction of free quetiapine and its major active metabolite is <5% excreted in the urine.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite and in the metabolism of its active metabolite norquetiapine.

### Age

Oral clearance of quetiapine was reduced by 40% in elderly patients (> 65 years, n = 9) compared to young patients (n = 12), and dosing adjustment may be necessary [see *Dosage and Administration* (2.3)].

### Gender

There is no gender effect on the pharmacokinetics of quetiapine.

### Race

There is no race effect on the pharmacokinetics of quetiapine.

### Smoking

Smoking has no effect on the oral clearance of quetiapine.

### Renal Insufficiency

Patients with severe renal impairment ( $\text{CL}_{\text{cr}}=10\text{-}30$  mL/min/ $1.73\text{m}^2$ , n=8) had a 25% lower mean oral clearance than normal subjects ( $\text{CL}_{\text{cr}}>80$  mL/min/ $1.73\text{m}^2$ , n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

### Hepatic Insufficiency

Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In 2 of the 8 hepatically impaired patients, AUC and C<sub>max</sub> were 3 times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed [see *Dosage and Administration* (2.3)].

### Drug-Drug Interactions

*In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin or ketoconazole [see *Dosage and Administration* (2.3) and *Drug Interactions* (7.1)].

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam [see *Drug Interactions* (7.2)].

## 13 NONCLINICAL TOXICOLOGY

### 13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose for schizophrenia and bipolar mania (800 mg/day) on a mg/m<sup>2</sup> basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m<sup>2</sup> basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m<sup>2</sup> basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m<sup>2</sup> basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or

0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m<sup>2</sup> basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-year toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown [see *Warnings and Precautions* (5.14)].

### Mutagenesis

The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

### Impairment of Fertility

Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m<sup>2</sup> basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m<sup>2</sup> basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m<sup>2</sup> basis. Drug-related effects included decreases in matings and in

matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m<sup>2</sup> basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m<sup>2</sup> basis.

### **13.2 Animal Toxicology and/or Pharmacology**

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2-year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m<sup>2</sup> basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m<sup>2</sup> basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose-related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta 8 cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m<sup>2</sup> basis.

## **14 CLINICAL STUDIES**

### **14.1 Schizophrenia**

The efficacy of SEROQUEL XR in the treatment of schizophrenia was demonstrated in 1 short-term, 6-week, fixed-dose, placebo-controlled trial of inpatients and outpatients with schizophrenia (n=573) who met DSM IV criteria for schizophrenia. SEROQUEL XR (once daily) was administered as 300 mg on Day 1, and the dose was increased to either 400 mg or 600 mg by Day 2, or 800 mg by Day 3. The primary endpoint was the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment (Day 42).

SEROQUEL XR doses of 400 mg, 600 mg and 800 mg once daily were superior to placebo in the PANSS total score at Day 42.

In a longer-term trial, clinically stable adult outpatients (n=171) meeting DSM-IV criteria for schizophrenia who remained stable following 16 weeks of open-label treatment with flexible doses of SEROQUEL XR (400 mg/day-800 mg/day) were randomized to placebo or to continue on their current SEROQUEL XR (400 mg/day-800 mg/day) for observation for possible relapse during the double-blind continuation (maintenance) phase. Stabilization during the open-label phase was defined as receiving a stable dose of SEROQUEL XR and having a CGI-S $\leq$ 4 and a PANSS score  $\leq$ 60 from beginning to end of this open-label phase (with no increase of  $\geq$ 10 points in PANSS total score). Relapse during the double-blind phase was defined in terms of a  $\geq$ 30% increase in the PANSS Total score, or CGI-Improvement score of  $\geq$ 6, or hospitalization due to worsening of schizophrenia, or need for any other antipsychotic medication. Patients on SEROQUEL XR experienced a statistically significant longer time to relapse than did patients on placebo.

## 14.2 Bipolar Disorder

### Bipolar Mania

The efficacy of SEROQUEL XR in the acute treatment of manic episodes was established in one 3-week, placebo-controlled trial in patients who met DSM-IV criteria for bipolar I disorder with manic or mixed episodes with or without psychotic features (N=316). Patients were hospitalized for a minimum of 4 days at randomization. Patients randomized to SEROQUEL XR received 300 mg on Day 1 and 600 mg on Day 2. Afterwards, the dose could be adjusted between 400 mg and 800 mg per day.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptoms in a range from 0 (no manic features) to 60 (maximum score). SEROQUEL XR was superior to placebo in the reduction of the YMRS total score at week 3.

The efficacy of SEROQUEL in the treatment of acute manic episodes was also established in 3 placebo-controlled trials in patients who met DSM-IV criteria for bipolar I disorder with manic episodes. These trials included patients with or without psychotic features and excluded patients with rapid cycling and mixed episodes. Of these trials, 2 were monotherapy (12 weeks) and 1 was adjunct therapy (3 weeks) to either lithium or divalproex. Key outcomes in these trials were change from

baseline in the YMRS score at 3 and 12 weeks for monotherapy and at 3 weeks for adjunct therapy. Adjunct therapy is defined as the simultaneous initiation or subsequent administration of SEROQUEL with lithium or divalproex.

The results of the trials follow:

#### *Monotherapy*

In two 12-week trials (n=300, n=299) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in the reduction of the YMRS total score at weeks 3 and 12. The majority of patients in these trials taking SEROQUEL were dosed in a range between 400 mg/day and 800 mg day.

#### *Adjunct Therapy*

In a 3-week placebo-controlled trial, 170 patients with bipolar mania (YMRS  $\geq$  20) were randomized to receive SEROQUEL or placebo as adjunct treatment to lithium or divalproex. Patients may or may not have received an adequate treatment course of lithium or divalproex prior to randomization. SEROQUEL was superior to placebo when added to lithium or divalproex alone in the reduction of YMRS total score. The majority of patients in this trial taking SEROQUEL were dosed in a range between 400 mg/day and 800 mg/day.

### **Depressive Episodes Associated with Bipolar Disorder**

The efficacy of SEROQUEL XR for the acute treatment of depressive episodes associated with bipolar disorder in patients who met DSM-IV criteria for bipolar disorder was established in one 8-week, randomized, double-blind, placebo-controlled study (N=280 outpatients). This study included patients with bipolar I and II disorder, and those with and without a rapid cycling course. Patients randomized to SEROQUEL XR were administered 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3, and 300 mg on Day 4 and after.

The primary rating instrument used to assess depressive symptoms was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with scores ranging from 0 (no depressive features) to 60 (maximum score). The primary endpoint was the change from baseline in MADRS score at week 8. SEROQUEL XR was superior to placebo in reduction of MADRS score at week 8.

The efficacy of SEROQUEL for the treatment of depressive episodes associated with bipolar disorder was established in 2 identical 8-week, randomized, double-blind, placebo-controlled studies (N=1045). These studies included patients with either bipolar I or II disorder and those with or without a rapid cycling course. Patients randomized to SEROQUEL were administered fixed doses of either 300 mg or 600 mg once daily.

The primary rating instrument used to assess depressive symptoms in these studies was the MADRS. The primary endpoint in both studies was the change from baseline in MADRS score at week 8. In both studies, SEROQUEL was superior to placebo in reduction of MADRS score at week 8. In these studies, no additional benefit was seen with the 600 mg dose. For the 300 mg dose group, statistically significant improvements over placebo were seen in overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q(SF).

### **Maintenance Treatment as an Adjunct to Lithium or Divalproex**

The efficacy of SEROQUEL in the maintenance treatment of bipolar I disorder was established in 2 placebo-controlled trials in patients (n=1326) who met DSM-IV criteria for bipolar I disorder. The trials included patients whose most recent episode was manic, depressed, or mixed, with or without psychotic features. In the open-label phase, patients were required to be stable on SEROQUEL plus lithium or divalproex for at least 12 weeks in order to be randomized. On average, patients were stabilized for 15 weeks. In the randomization phase, patients continued treatment with lithium or divalproex and were randomized to receive either SEROQUEL (administered twice daily totaling 400 mg/day to 800 mg/day or placebo. Approximately 50% of the patients had discontinued from the SEROQUEL group by day 280 and 50% of the placebo group had discontinued by day 117 of double-blind treatment. The primary endpoint in these studies was time to recurrence of a mood event (manic, mixed or depressed episode). A mood event was defined as medication initiation or hospitalization for a mood episode; YMRS score  $\geq 20$  or MADRS score  $\geq 20$  at 2 consecutive assessments; or study discontinuation due to a mood event.

In both studies, SEROQUEL was superior to placebo in increasing the time to recurrence of any mood event. The treatment effect was present for increasing time to recurrence of both manic and depressed episodes. The effect of SEROQUEL was independent of any specific subgroup (assigned mood stabilizer, sex, age, race, most recent bipolar episode, or rapid cycling course).

### **14.3 Major Depressive Disorder, Adjunctive Therapy to Antidepressants**

The efficacy of SEROQUEL XR as adjunctive therapy to antidepressants in the treatment of MDD was demonstrated in two 6-week placebo-controlled, fixed-dose trials (n=936). SEROQUEL XR 150 mg/day or 300 mg/day was given as adjunctive therapy to existing

antidepressant therapy in patients who had previously shown an inadequate response to at least one antidepressant. SEROQUEL XR was administered as 50 mg/day on Days 1 and 2, and increased to 150 mg/day on Day 3 for both dose groups. On Day 5, the dose was increased to 300 mg/day in the 300 mg/day fixed-dose group. Inadequate response was defined as having continued depressive symptoms for the current episode (HAM-D total score of  $\geq 20$ ) despite using an antidepressant for 6 weeks at or above the minimally effective labelled dose. The mean HAM-D total score at entry was 24, and 17% of patients scored 28 or greater. Patients were on various antidepressants prior to study entry including SSRI's (paroxetine, fluoxetine, sertraline escitalopram, or citalopram), SNRI's, (duloxetine and venlafaxine,) TCA (amitryptiline) and other (bupropion).

The primary endpoint in these trials was change from baseline to week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale used to assess the degree of depressive symptomatology (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts) with total scores ranging from 0 (no depressive features) to 60 (maximum score).

SEROQUEL XR 300 mg once daily as adjunctive treatment to other antidepressant therapy was superior to antidepressant alone in reduction of MADRS total score in both trials. SEROQUEL XR 150 mg once daily as adjunctive treatment was superior to antidepressant therapy alone in reduction of MADRS total score in one trial.

## **15 REFERENCES**

None

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

- 50 mg Tablets (NDC 0310-0280) peach, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 50" on one side and plain on the other are supplied in bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.
- 150 mg Tablets (NDC 0310-0281) white, film-coated, capsule-shaped, biconvex, intagliated tablet with 'XR 150' on one side and plain on the other are supplied in bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.
- 200 mg Tablets (NDC 0310-0282) yellow, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 200" on one side and

plain on the other are supplied in bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.

- 300 mg Tablets (NDC 0310-0283) pale yellow, film coated, capsule-shaped, biconvex, intagliated tablet with “XR 300” on one side and plain on the other are supplied in bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.
- 400 mg Tablets (NDC 0310-0284) white, film coated, capsule-shaped, biconvex, intagliated tablet with “XR 400” on one side and plain on the other are supplied in bottles of 60 tablets and hospital unit dose packages of 100 tablets.

Store SEROQUEL XR at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

## **17 PATIENT COUNSELING INFORMATION**

### **17.1 Information for Patients**

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL XR and should counsel them in its appropriate use. A patient Medication Guide about “Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions” is available for SEROQUEL XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SEROQUEL XR.

#### **Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. Quetiapine is not approved for elderly patients with dementia-related psychosis [*see Warnings and Precautions (5.1)*].

#### **Clinical Worsening and Suicide Risk**

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia,

irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [*see Warnings and Precautions (5.2)*].

### Neuroleptic Malignant Syndrome (NMS)

Patients should be advised to report to their physician any signs or symptoms that may be related to NMS. These may include muscle stiffness and high fever [*see Warnings and Precautions (5.3)*].

### Hyperglycemia and Diabetes Mellitus

Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should have their blood glucose monitored at the beginning of and periodically during treatment [*see Warnings and Precautions (5.4)*].

### Hyperlipidemia

Patients should be advised that elevations in total cholesterol, LDL-cholesterol and triglycerides and decreases in HDL-cholesterol may occur. Patients should have their lipid profile monitored at the beginning of and periodically during treatment [*see Warnings and Precautions (5.5)*].

### Weight Gain

Patients should be advised that they may experience weight gain. Patients should have their weight monitored regularly [*see Warnings and Precautions (5.6)*].

### Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing, which may lead to falls) especially during the period of initial dose titration, and also at times of re-initiating treatment or increases in dose [*see Warnings and Precautions (5.8)*].

### Increased Blood Pressure in Children and Adolescents

Blood pressure should be measured at the beginning of, and periodically during, treatment [see *Warnings and Precautions* (5.9)].

#### Leukopenia/Neutropenia

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking SEROQUEL XR [see *Warnings and Precautions* (5.10)].

#### Interference with Cognitive and Motor Performance

Patients should be advised of the risk of somnolence or sedation (which may lead to falls), especially during the period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating machinery, until they are reasonably certain quetiapine therapy does not affect them adversely. Patients should limit consumption of alcohol during treatment with quetiapine [see *Warnings and Precautions* (5.16)].

#### Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration [see *Warnings and Precautions* (5.18)].

#### Concomitant Medication

As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs [see *Warnings and Precautions* (5.21)].

#### Pregnancy and Nursing

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised not to breast feed if they are taking quetiapine [see *Use in Specific Populations* (8.1 and 8.3)].

## 17.2 Medication Guide

**[The Medication Guides should be as similar as possible for SEROQUEL and SEROQUEL XR].**

Medication Guide

SEROQUEL XR (SER-oh-kwell)

(quetiapine fumarate)

Extended-Release Tablets

Read this Medication Guide before you start taking SEROQUEL XR and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

### **What is the most important information I should know about SEROQUEL XR?**

**Serious side effects may happen when you take SEROQUEL XR, including:**

- **Risk of death in the elderly with dementia: Medicines like SEROQUEL XR can raise the risk of death in elderly people who have lost touch with reality due to confusion and memory loss (dementia).** SEROQUELXR is not approved for treating psychosis in the elderly with dementia.
- **Risk of suicidal thoughts or actions: Antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions:**
  1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
  2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) depression, bipolar illness (also called manic-depressive illness), or suicidal thoughts or actions.
  3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

**Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:**

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

**What else do I need to know about antidepressant medicines?**

• **Never stop an antidepressant medicine without first talking to your healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.

• **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

• **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.

• **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member take. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

• **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

**What is SEROQUEL XR?**

- SEROQUEL XR is a prescription medicine used to treat schizophrenia in adults.
- SEROQUEL XR is a prescription medicine used to treat bipolar disorder in adults, including:
  - manic episodes associated with bipolar disorder alone or with lithium or divalproex.
  - depressive episodes associated with bipolar disorder.
  - long-term treatment of bipolar I disorder with lithium or divalproex.
- SEROQUEL XR is a prescription medicine used to treat major depressive disorder as add-on treatment with antidepressant medicines when your doctor determines that one antidepressant alone is not enough to treat your depression.

SEROQUEL XR is not approved for patients under 18 years of age.

### **What should I tell my healthcare provider before taking SEROQUEL XR?**

Before taking SEROQUEL XR, tell your healthcare provider if you have or have had:

- diabetes or high blood sugar in you or your family: your healthcare provider should check your blood sugar before you start SEROQUEL XR and also during therapy.
- high levels of total cholesterol, triglycerides or LDL-cholesterol or low levels of HDL- cholesterol
- low or high blood pressure
- low white blood cell count
- cataracts
- seizures
- abnormal thyroid tests
- high prolactin levels
- heart problems
- liver problems
- any other medical condition
- pregnancy or plans to become pregnant. It is not known if SEROQUEL XR will harm your unborn baby.
- breast-feeding or plans to breast-feed. It is not known if SEROQUEL XR will pass into your breast milk. You and your healthcare provider should decide if you will take SEROQUEL XR or breast-feed. You should not do both.

**Tell the healthcare provider about all the medicines that you take or recently have taken** including prescription medicines, non-prescription medicines, herbal supplements and vitamins.

SEROQUEL XR and other medicines may affect each other causing serious side effects. SEROQUEL XR may affect the way other medicines work, and other medicines may affect how SEROQUEL XR works.

Especially tell your healthcare provider if you take or plan to take medicines for:

- depression
- high blood pressure
- Parkinson's disease
- trouble sleeping

Also tell your healthcare provider if you take or plan to take any of these medicines:

- phenytoin, divalproex or carbamazepine (for epilepsy)
- barbiturates (to help you sleep)
- rifampin (for tuberculosis)
- glucocorticoids (steroids for inflammation)
- thioridazine (an antipsychotic)
- ketoconazole, fluconazole or itraconazole (for fungal infections)
- erythromycin (an antibiotic)
- protease inhibitors (for HIV)

This is not a complete list of medicines that can affect or be affected by SEROQUEL XR. Your doctor can tell you if it is safe to take SEROQUEL XR with your other medicines. Do not start or stop any medicines while taking SEROQUEL XR without talking to your healthcare provider first. Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

### **How should I take SEROQUEL XR?**

- Take SEROQUEL XR exactly as your healthcare provider tells you to take it. Do not change the dose yourself.
- Take SEROQUEL XR by mouth, with a light meal or without food.

- SEROQUEL XR should be swallowed whole and not split, chewed or crushed.
- If you feel you need to stop SEROQUEL XR, talk with your healthcare provider first.

If you suddenly stop taking SEROQUEL XR, you may experience side effects such as trouble sleeping or trouble staying asleep (insomnia), nausea, and vomiting.

- If you miss a dose, take it as soon as you remember. If it is close to the next dose, skip the missed dose. Just take the next dose at your regular time. Do not take 2 doses at the same time unless your healthcare provider tells you to. If you are not sure about your dosing, call your healthcare provider.
- If you take too much SEROQUEL XR, call your healthcare provider or poison control center at 1-800-222-1212 right away or go to the nearest hospital emergency room.

### **What should I avoid while taking SEROQUEL XR?**

Do not drive, operate machinery, or do other dangerous activities until you know how SEROQUEL XR affects you. SEROQUEL XR may make you drowsy.

- Avoid getting over-heated or dehydrated.
  - Do not over-exercise.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun. Do not wear too much or heavy clothing.
  - Drink plenty of water.
- Do not drink alcohol while taking SEROQUEL XR. It may make some side effects of SEROQUEL XR worse.

### **What are possible side effects of SEROQUEL XR?**

**Serious side effects have been reported with SEROQUEL XR including:**

**Also see “What is the most important information I should know about SEROQUEL XR?” at the beginning of this Medication Guide**

- **Neuroleptic malignant syndrome (NMS):** Tell your healthcare provider right away if you have some or all of the

following symptoms: high fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and blood pressure. These may be symptoms of a rare and serious condition that can lead to death. Stop SEROQUEL XR and call your healthcare provider right away.

- **High blood sugar (hyperglycemia):** Increases in blood sugar can happen in some people who take SEROQUEL XR. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes) your healthcare provider should check your blood sugar before you start SEROQUEL XR and during therapy.

Call your healthcare provider if you have any of these symptoms of high blood sugar while taking SEROQUEL XR:

- feel very thirsty
  - need to urinate more than usual
  - feel very hungry
  - feel weak or tired
  - feel sick to your stomach
  - feel confused, or your breath smells fruity.
- **High cholesterol and triglyceride levels in the blood (fat in the blood)** Increases in total cholesterol, triglycerides and LDL (bad) cholesterol and decreases in HDL (good) cholesterol have been reported in clinical trials with SEROQUEL XR. You may not have any symptoms, so your healthcare provider should do blood tests to check your cholesterol and triglyceride levels before you start taking SEROQUEL XR and during therapy.
  - **Increase in weight (weight gain):** Weight gain has been seen in patients who take SEROQUEL XR so you and your healthcare provider should check your weight regularly.
  - **Tardive dyskinesia:** Tell your healthcare provider about any movements you cannot control in your face, tongue, or other body parts. These may be signs of a serious condition. Tardive dyskinesia may not go away, even if you stop taking SEROQUEL XR. Tardive dyskinesia may also start after you stop taking SEROQUEL XR.

- **Orthostatic hypotension (decreased blood pressure):** lightheadedness or fainting caused by a sudden change in heart rate and blood pressure when rising too quickly from a sitting or lying position.
- **Increases in blood pressure:** reported in children and teenagers. Your healthcare provider should check blood pressure in children and adolescents before starting SEROQUEL XR and during therapy. SEROQUEL XR is not approved for patients under 18 years of age.
- **Low white blood cell count**
- **Cataracts**
- **Seizures**
- **Abnormal thyroid tests:** Your healthcare provider may do blood tests to check your thyroid hormone level.
- **Increases in prolactin levels:** Your healthcare provider may do blood test to check your prolactin levels.
- **Increases in liver enzymes:** Your healthcare provider may do blood test to check your liver enzyme levels.
- **Long lasting and painful erection**
- **Difficulty swallowing**

**Common possible side effects with SEROQUEL XR include:**

- drowsiness
- dry mouth
- constipation
- dizziness
- increased appetite
- upset stomach
- weight gain
- fatigue
- disturbance in speech and language
- abdominal pain
- stuffy nose

These are not all the possible side effects of SEROQUEL XR. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store SEROQUEL XR?**

- Store SEROQUEL XR at room temperature, between 59°F to 86°F (15°C to 30°C).
- Keep SEROQUEL XR and all medicines out of the reach of children.

### **General information about SEROQUEL XR**

Do not take SEROQUEL unless your healthcare provider has prescribed it for you for your condition. Do not share SEROQUEL XR with other people, even if they have the same condition. It may harm them.

This Medication Guide provides a summary of important information about SEROQUEL XR. For more information about SEROQUEL XR, talk with your healthcare provider or pharmacist or call 1-800-236-9933. You can ask your healthcare provider for information about SEROQUEL XR that is written for health professionals.

### **What are the ingredients in SEROQUEL XR?**

**Active ingredient:** quetiapine fumarate

**Inactive ingredients:** lactose monohydrate, microcrystalline cellulose, sodium citrate, hypromellose, and magnesium stearate. The film coating for all SEROQUEL XR tablets contain hypromellose, polyethylene glycol 400 and titanium dioxide. In addition yellow iron oxide (50, 200 and 300 mg tablets) and red iron oxide (50 tablets) are included in the film coating of specific strengths.

### **The symptoms of Schizophrenia include:**

- Having lost touch with reality (psychosis),
- Seeing things that are not there or hearing voices (hallucinations),
- Believing things that are not true (delusions) and
- Being suspicious (paranoia).

### **The symptoms of Bipolar Disorder include:**

- General symptoms of bipolar disorder include: extreme mood swings, along with other specific symptoms and behaviors. These mood swings, or "episodes," include manic (highs) and depressive (lows).

- Common symptoms of a manic episode include: feeling extremely happy, being very irritable, restless, talking too fast and too much, and having more energy and needing less sleep than usual.
- Common symptoms of a depressive episode include: feelings of sadness or emptiness, increased tearfulness, a loss of interest in activities you once enjoyed, loss of energy, difficulty concentrating or making decisions, feelings of worthlessness or guilt, changes in sleep or appetite and
- Thoughts of death or suicide.

**The symptoms of Major Depressive Disorder (MDD) include:**

- Feeling of sadness, emptiness and increase tearfulness,
- Loss of interest in activities that you once enjoyed and loss of energy
- Problems focusing and making decisions,
- Feeling of worthlessness or guilt
- Changes in sleep or eating patterns
- Thoughts of death or suicide.
- MDD symptoms last most of the day, nearly every day for at least two weeks, and interfere with daily life at home and at work

**This Medication Guide has been approved by the U.S. Food and Drug Administration.**

SEROQUEL XR is a trademark of the AstraZeneca group of companies.

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SIC XXXX-XX

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 22-047/S-011**

**REMS**

## **REMS**

**NDA 22-047**  
**SEROQUEL<sup>®</sup> XR (quetiapine fumarate) Extended-Release Tablets**  
**Atypical Antipsychotic**  
**AstraZeneca Pharmaceuticals LP**  
**1800 Concord Pike**  
**P.O. Box 8355**  
**Wilmington, DE 19803-8355**

**Contact: The Information Center at AstraZeneca**  
**1-800-236-9933**

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

#### **I. GOAL:**

The goal of this REMS is to inform patients about the serious risks associated with the use of SEROQUEL XR<sup>®</sup> (quetiapine fumarate) Extended-Release Tablets.

#### **II. REMS ELEMENTS:**

##### **A. Medication Guide**

A Medication Guide will be dispensed with each SEROQUEL XR prescription. In accordance with 21 CFR 208.24(b), AstraZeneca Pharmaceuticals LP (AstraZeneca) will make the Medication Guide available for distribution to patients by providing the means to permit authorized dispensers to produce the Medication Guides in sufficient numbers to meet the dispenser obligations under 21 CFR 208.24(e) to provide a Medication Guide to each patient receiving a prescription for SEROQUEL XR.

In accordance with 21 CFR 208.24(d) a statement will be included on the container label for SEROQUEL XR to alert pharmacists to dispense the Medication Guide with each prescription of the product. The following statement will be included on the container label, “Medication Guide must be dispensed to patients.”

##### **B. Timetable for Submission of Assessments**

AstraZeneca will submit REMS Assessments to FDA 18 months, 3 years and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. AstraZeneca will submit each assessment so it will be received by the FDA on or before the due date.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

**OFFICE DIRECTOR MEMO**

**MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** December 2, 2009

**FROM:** Thomas P. Laughren, M.D.  
Director, Division of Psychiatry Products  
HFD-130

**SUBJECT:** Recommendation for [REDACTED] (b) (4)  
[REDACTED] approval  
action for Seroquel (quetiapine) XR tablets for adjunctive therapy of depressive  
episodes associated with major depressive disorder (based on short-term data)

**TO:** File NDA 22-047 (b) (4)/011 (b) (4)  
[Note: This overview should be filed with the 6-2-09 re-submission of [REDACTED] (b) (4).]

**1.0 BACKGROUND**

Seroquel (quetiapine immediate release) is an atypical antipsychotic that is approved (1) as monotherapy for the treatment of schizophrenia, (2) as monotherapy and as adjunctive therapy to lithium or valproate for the acute treatment of manic episodes associated with bipolar disorder, (3) as monotherapy for the acute treatment of depressive episodes associated with bipolar disorder, and (4) as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar disorder. The extended release formulation of quetiapine (i.e., Seroquel XR) is approved (1) as monotherapy for the treatment of schizophrenia, (2) as monotherapy for the acute treatment of bipolar depression and mania, and (3) as adjunctive therapy for the acute treatment of bipolar mania.

These supplements, originally submitted 2-27-08, provided data in support of claims for Seroquel XR for monotherapy (based on both short-term and maintenance data), and adjunctive therapy (based on short-term data), of depressive episodes associated with major depressive disorder.

The sponsor's proposed dose range of Seroquel XR for major depressive disorder is 50 to 300 mg/day for monotherapy and 150 to 300 mg/day for adjunctive therapy.

The primary review of the efficacy and safety data was done by Earl Hearst, M.D., from the clinical group. Phillip Dinh, Ph.D., from the biometrics group, also reviewed the efficacy data.

We issued a CR letter for these supplements on 12-22-08. In that letter, we acknowledged that the sponsor had demonstrated efficacy for Seroquel XR for all the claims sought. We also, however, raised a concern about the longer term risks of using this drug in the population of patients with MDD. We indicated that these risks had not been adequately addressed in the application. We particularly focused on the metabolic risks (hyperglycemia/diabetes, hyperlipidemia, and weight gain) and the risk for tardive dyskinesia. We asked that they address these risks, because a risk benefit analysis would be integral to any discussion of the use of Seroquel XR for a common, non-psychotic disorder such as MDD. We noted that, while MDD is an accepted target for pharmacotherapy, there are multiple effective therapies approved for the treatment of MDD that do not have the same longer term safety risks. We suggested that they might include data from observational databases, post-marketing data, and literature data to elucidate these longer-term risks of using Seroquel XR.

We subsequently decided to take this application to the Psychopharmacological Drugs Advisory Committee (PDAC). This committee recommended in favor of an approval for the adjunctive claim, but not the monotherapy claim. The detailed results of that meeting will be discussed later in this memo.

Subsequent to the PDAC meeting, the sponsor responded to the 12-22-08 CR letter with a 6-2-09 submission. This included much of the same data the sponsor had submitted for the 4-8-09 PDAC meeting in support of its argument that Seroquel XR is safe enough to justify use in (b) (4) adjunctive therapy for MDD. These data were considered at the 4-8-09 PDAC meeting, and thus, there was not much additional review work needed to address this resubmission.

## **2.0 CHEMISTRY**

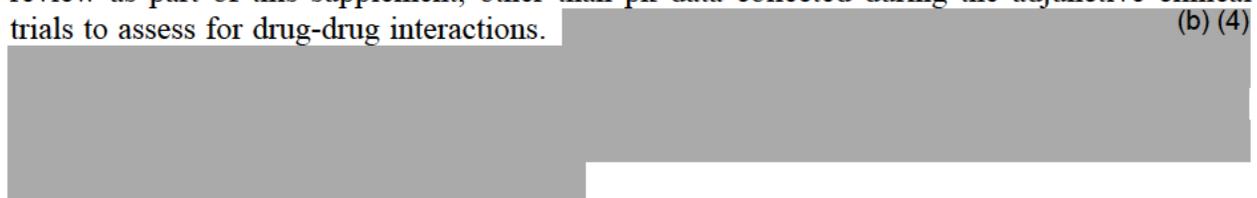
Seroquel XR is an approved product, and there were no CMC issues that required review as part of this supplement, except for an environmental assessment for which a request for categorical exclusion was made and accepted.

## **3.0 PHARMACOLOGY**

Seroquel XR is an approved product. There were no pharm/tox issues that required review as part of these supplements.

#### **4.0 BIOPHARMACEUTICS**

Seroquel XR is an approved product, and there were no biopharmaceutics issues that required review as part of this supplement, other than pk data collected during the adjunctive clinical trials to assess for drug-drug interactions. (b) (4)



#### **5.0 CLINICAL DATA**

##### **5.1 Efficacy Data**

###### **5.1.1 Overview of Studies Pertinent to Efficacy**

The sponsor submitted 7 studies in support of its new claims in MDD, including 4 short-term monotherapy studies (studies 1, 2, 3, and 4), 2 short-term adjunctive therapy studies (studies 6 and 7), and a randomized withdrawal study (study 5). For all short-term studies, change from baseline to endpoint on the total MADRS score was the primary endpoint. All of the short-term studies were randomized, double-blind, parallel group, placebo-controlled trials in adult outpatients meeting DSM-IV criteria for MDD. Studies 1, 2, 6, and 7 were fixed dose studies, while studies 3 and 4 were flexible dose. Studies 2 and 4 included an active control arm.

(b) (4)



### Short-Term Adjunctive Therapy Studies

-Study 6 was a 6-week fixed dose US study including fixed Seroquel XR doses of 150 and 300 mg/day, added on to a stable dose of one of several other antidepressant products. Only the 300 mg/day dose was superior to placebo (Pbo: -11.7; 150 mg: -13.6; 300 mg: -14.7).

-Study 7 was a 6-week fixed dose US study including fixed Seroquel XR doses of 150 and 300 mg/day, added on to a stable dose of one of several other antidepressant products. Both doses were superior to placebo, with no numerical advantage for the 300 mg/day dose over the 150 mg/day dose (Pbo: -12.2; 150 mg: -15.3; 300 mg: -14.9).

(b) (4)

### **5.1.2 Comment on Other Important Clinical Issues Regarding Efficacy**

#### Evidence Bearing on the Question of Dose/Response for Efficacy

(b) (4)

For adjunctive therapy studies, the 300 mg/day dose was superior to placebo in 2 studies, and the 150 mg/day superior in only 1 of the 2 studies. Therefore, the proposed dose range of 150-300 mg/day seems reasonable.

#### Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis age, gender, and race. There was no indication of any difference in effectiveness based on these analyses.

## Size of Treatment Effect

The effect sizes as measured by the difference between drug and placebo in change from baseline on the MADRS were similar to effect sizes seen in other positive trials.

(b) (4)

## PREA Requirements

(b) (4)

question is whether or not adjunctive studies are needed in the pediatric population. At the current time, there are only 2 drugs approved for treating pediatric MDD, i.e., fluoxetine and escitalopram, both SSRIs. Thus, the argument for an adjunctive study in pediatric patients is quite weak. Requiring such a study would imply that we think it might be a good therapeutic strategy to move to adding on an atypical antipsychotic agent in pediatric patients who fail to respond adequately to one of these agents. In fact, this would not be the logical choice. Most clinicians would move first to another class of antidepressant, e.g., and SNRI or bupropion. The sponsor has requested a waiver for all pediatric patients, and I agree this is appropriate. Thus we will waive this requirement for all pediatric age groups.

### **5.1.3 Conclusions Regarding Efficacy Data**

The sponsor has, in my view, provided sufficient evidence to support claims for (b) (4) adjunctive therapy for Seroquel XR in MDD. (b) (4)

### **5.2 Safety Data**

The safety review for these supplements was based on data from the 6 acute studies and the maintenance study. Overall, the safety findings for these supplements were consistent with the known adverse event profile for quetiapine and no important new adverse events that could be considered causally related to quetiapine were discovered as a result of the safety review. We have also reviewed a comprehensive submission from the sponsor regarding metabolic effects of quetiapine. I agree that the safety profile we are seeing in the MDD population is not different from the profile we have already observed in other populations. However, it is of considerable concern that approving (b) (4) adjunctive claims would likely greatly expand the use of this product. There is a particular concern regarding longer-term risks which are not yet fully established. Tardive dyskinesia is an accepted risk in schizophrenic and bipolar patients, and in fact, thought to be somewhat reduced in association with atypical antipsychotic drugs,

such as quetiapine. Nevertheless, there remains a concern that some fraction of patients exposed to quetiapine long-term may experience this adverse event. Furthermore, there is accumulating evidence that quetiapine may have substantial metabolic risks (weight gain, hyperlipidemia, and hyperglycemia) with all the attendant longer-term cardiovascular and other risks. In addition, there is concern for a possible risk of sudden cardiac death associated with the use of atypical antipsychotic drugs. This concern was raised in a recent paper by Wayne Ray. All three concerns were discussed at the 4-8-09 PDAC meeting, (see later, under PDAC discussion).

Concern about possibly undisclosed data raised by a consumer: FDA received an inquiry from a consumer who raised a general question of whether or not FDA has in its possession all the relevant safety data it needs to make final decisions about pending applications from several manufacturers whose products were involved in certain tort litigation. This consumer referred to pending tort litigation in New Jersey involving three atypical antipsychotic drugs, including Seroquel. Allegedly a 3-judge panel was appointed to give an opinion on whether the documents involved should be made publically available, and this panel presumably recommended that the documents be released. The consumer has alleged that the documents have remained sealed, however, because of an objection by one of the manufacturers involved in this case. The consumer has raised the question of whether or not FDA has access to any such sealed documents and has had an opportunity to examine them. The consumer has urged FDA to request these documents from the companies involved.

We issued a letter to Astra Zeneca (AZ) asking them to submit to the agency all data and information regarding any quetiapine products involved in the New Jersey case in question. If there were no documents or other information from AZ that were involved in this litigation, we asked that they formally assert that by return letter. AZ did submit such a letter, and I now consider this matter resolved.

### **5.3 Clinical Sections of Labeling**

We have made a number of modifications to the sponsor's proposed labeling and asked them to make a number of additional modifications. We have now reached agreement on final labeling.

## **6.0 WORLD LITERATURE**

The sponsor has provided an updated literature review. Dr. Hearst has examined this review and has concluded that it reveals no new safety information.

## **7.0 FOREIGN REGULATORY ACTIONS**

To my knowledge, Seroquel XR is not approved in any other countries for the treatment of MDD.

## **8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING**

At this 4-8-09 meeting, the sponsor presented the safety and efficacy data it considered sufficient to support the approval of both the monotherapy and adjunctive claims for Seroquel XR in MDD. In order to address FDA's concerns about longer-term risks, the sponsor pooled data across all of its studies. They argued that, based on their accumulated data, there is not a strong suggestion of an important risk of longer-term metabolic consequences for patients taking quetiapine at the lower doses needed to treat MDD. They similarly argued that their data suggested a rather low risk of TD (they estimated 0.2%; 53/26,454). As noted, the concern about possible sudden cardiac death with atypical antipsychotics came from a retrospective cohort study by Wayne Ray. The sponsor tried to address this with a pooled analysis of its own quetiapine data, and argued that their analysis did not support such a concern.

The PDAC considered the sponsor's arguments, but remained unconvinced that they had made a sufficient case to justify approving Seroquel XR as monotherapy for MDD. Their concern, one I share, is that the data from the sponsor's program are simply not sufficient to address the longer-term safety concerns. In the absence of sufficient data, they felt that it would not be appropriate at this time to recommend an approval of the monotherapy claim. They did, however, recommend that the data are sufficient to support an approval of the adjunctive claim. They did acknowledge that for certain patients, e.g., those who fail to respond at all to multiple trials of available antidepressants, or who are intolerant to available antidepressants, a trial of Seroquel XR as monotherapy might be appropriate. (b) (4)



## **9.0 DSI INSPECTIONS**

Inspections were conducted at three sites that enrolled patients from pivotal studies. The data from these sites were deemed to be acceptable.

## **10.0 LABELING AND ACTION LETTERS**

As noted, we have now reached agreement on final labeling.

## **11.0 CONCLUSIONS AND RECOMMENDATIONS**

The sponsor has submitted sufficient data to support the conclusion that Seroquel XR is effective as (b) (4) adjunctive therapy in the treatment of MDD. The safety profile, to the

extent that it can be characterized, appears to be similar to that observed with this drug in other conditions. However, there remains a concern about longer-term risks with this drug, in particular risks related to metabolic changes with this drug, the possibility of tardive dyskinesia, and a concern about possible sudden cardiac death. These issues become even more important as the distribution of this drug to a much broader patient population is considered. Thus, in agreement with the PDAC who met to discuss these applications on 4-8-09, [REDACTED] (b) (4) [REDACTED] an approval letter for the adjunctive claim. [REDACTED] (b) (4) [REDACTED] We have now reached agreement with the sponsor on final labeling regarding the adjunctive claim.

cc:

Orig NDA 22-047S [REDACTED] (b) (4) /011 [REDACTED] (b) (4)

HFD-130

HFD-130/TLaughren/MMathis/RLevin/EHearst/JToure/RGrewal

DOC: Laughren\_NDA22047\_S [REDACTED] (b) (4) -011 [REDACTED] (b) (4) \_Seroquel XR\_Action Memo.doc

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

(b) (4)

NDA-22047

SUPPL-11

ASTRAZENECA  
PHARMACEUTICA  
LS LP

SEROQUEL XR

(b) (4)

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THOMAS P LAUGHREN  
12/02/2009

**MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** December 21, 2008

**FROM:** Thomas P. Laughren, M.D.  
Director, Division of Psychiatry Products  
HFD-130

**SUBJECT:** Recommendation for Complete Response action for Seroquel (quetiapine) XR tablets for acute monotherapy, acute adjunctive therapy, and maintenance monotherapy of depressive episodes associated with major depressive disorder

**TO:** File NDA 22-047/S-010/011/012  
[Note: This overview should be filed with the 2-27-08 original submission of these supplements.]

**1.0 BACKGROUND**

Seroquel (quetiapine immediate release) is an atypical antipsychotic that is approved (1) as monotherapy for the acute treatment of schizophrenia, (2) as monotherapy and as adjunctive therapy to lithium or valproate for the acute treatment of manic episodes associated with bipolar disorder, (3) as monotherapy for the acute treatment of depressive episodes associated with bipolar disorder, and (4) as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar disorder. The extended release formulation of quetiapine (i.e., Seroquel XR) is approved (1) as monotherapy for the acute and maintenance treatment of schizophrenia, (2) as monotherapy for the acute treatment of bipolar depression and mania, and (3) as adjunctive therapy for the acute treatment of bipolar mania.

This supplement provides data in support of claims for Seroquel XR for acute monotherapy, acute adjunctive therapy, and maintenance monotherapy of depressive episodes associated with major depressive disorder.

The sponsor's proposed dose range of Seroquel XR for major depressive disorder is 50 to 300 mg/day.

The primary review of the efficacy and safety data was done by Earl Hearst, M.D., from the clinical group. Phillip Dinh, Ph.D., from the biometrics group, also reviewed the efficacy data.

We decided not to take this application to the Psychopharmacological Drugs Advisory Committee (PDAC).

## **2.0 CHEMISTRY**

Seroquel XR is an approved product, and there were no CMC issues that required review as part of this supplement, except for an environmental assessment for which a request for categorical exclusion was made and accepted.

## **3.0 PHARMACOLOGY**

Seroquel XR is an approved product. There were no pharm/tox issues that required review as part of these supplements.

## **4.0 BIOPHARMACEUTICS**

Seroquel XR is an approved product, and there were no biopharmaceutics issues that required review as part of this supplement, other than pk data collected during the adjunctive clinical trials to assess for drug-drug interactions. Based on these data, OCP recommended a paragraph for labeling suggesting that, although no clear effect of Seroquel XR on co-administered antidepressant levels was demonstrated, there was wide inter-patient variability, and close monitoring is advised.

## **5.0 CLINICAL DATA**

### **5.1 Efficacy Data**

#### **5.1.1 Overview of Studies Pertinent to Efficacy**

The sponsor submitted 7 studies in support of its new claims in MDD, including 4 short-term monotherapy studies in support of an acute monotherapy claim (studies 1, 2, 3, and 4), 2 short-term adjunctive therapy studies in support of an acute adjunctive therapy claim (studies 6 and 7), and a randomized withdrawal study (study 5) in support of a maintenance monotherapy claim. For all short-term studies, change from baseline to endpoint on the total MADRS score was the primary endpoint. All of the short-term studies were randomized, double-blind, parallel group, placebo-controlled trials in adult outpatients meeting DSM-IV criteria for MDD. Studies 1, 2, 6, and 7 were fixed dose studies, while studies 3 and 4 were flexible dose. Studies 2 and 4 included an active control arm.

### Acute Monotherapy Studies

-Study 1 was a 6-week fixed dose US study including fixed Seroquel XR doses of 50, 150, and 300 mg/day. All 3 doses in Study 1 were superior to placebo, with only a slight numerical advantage for the 150 mg/day dose vs the 50 mg/day dose (Pbo: -11.1; 50 mg: -13.6; 150 mg: -14.5), and no numerical advantage for the 300 mg/day dose over the 150 mg/day dose (150 mg: -14.5; 300 mg: -14.2).

-Study 2 was a 6-week fixed dose US study including fixed Seroquel XR doses of 150 and 300 mg/day. Both doses were superior to placebo, with only a slight numerical advantage for the 300 mg/day dose over the 150 mg/day dose (Pbo: -11.2; 150 mg: -14.8; 300 mg: -15.3). Duloxetine was also superior to placebo.

-Study 3 was an 8-week flexible dose US study (Seroquel XR doses ranging from 150 to 300 mg/day). Seroquel XR was superior to placebo (Pbo: -13.1; Seroquel XR: -16.5; mean daily dose was 162 mg/day).

-Study 4 was an 8-week flexible dose non-US study (Seroquel XR doses ranging from 150 to 300 mg/day). Neither Seroquel XR nor the active control (escitalopram) was superior to placebo, i.e., this was a failed study.

### Acute Adjunctive Therapy Studies

-Study 6 was a 6-week fixed dose US study including fixed Seroquel XR doses of 150 and 300 mg/day, added on to a stable dose of one of several other antidepressant products. Only the 300 mg/day dose was superior to placebo (Pbo: -11.7; 150 mg: -13.6; 300 mg: -14.7).

-Study 7 was a 6-week fixed dose US study including fixed Seroquel XR doses of 150 and 300 mg/day, added on to a stable dose of one of several other antidepressant products. Both doses were superior to placebo, with no numerical advantage for the 300 mg/day dose over the 150 mg/day dose (Pbo: -12.2; 150 mg: -15.3; 300 mg: -14.9).

### Maintenance Study (Study 5)

This was a randomized withdrawal study involving an open stabilization period of at least 12 weeks of acute treatment with Seroquel XR (dose range of 50 to 300 mg/day; mean dose was 177 mg/day) in patients with MDD. Responders during the open label phase were randomized to either continue on Seroquel XR or receive placebo, and they were observed for relapse for up to 52 weeks. Time to depressive relapse was statistically significantly increased in patients randomized to continued treatment with Seroquel XR (Hazard Ratio = 0.36;  $p < 0.001$ ). The relapse rates were 15% for Seroquel XR vs 34% for placebo.

### **5.1.2 Comment on Other Important Clinical Issues Regarding Efficacy**

#### Evidence Bearing on the Question of Dose/Response for Efficacy

For the acute monotherapy studies, all 3 doses studied were superior to placebo, however, there was only a slight numerical advantage for the higher doses compared to the lower doses, and this was not consistently demonstrated. Nevertheless, given the suggestion at least of a possible advantage of higher doses and the fact that there was only 1 demonstration of efficacy at the 50 mg/day dose, it seems reasonable to recommend dosing within a range of 50-300 mg/day, but with cautionary language suggesting that there is no clear demonstration of an advantage of higher doses, and there are clearly dose-dependent adverse events.

For adjunctive therapy studies, the 300 mg/day dose was superior to placebo in 2 studies, and the 150 mg/day superior in only 1 of the 2 studies. Therefore, the proposed dose range of 150-300 mg/day seems reasonable.

#### Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis age, gender, and race. There was no indication of any difference in effectiveness based on these analyses.

#### Size of Treatment Effect

The effect sizes as measured by the difference between drug and placebo in change from baseline on the MADRS were similar to effect sizes seen in other positive trials.

#### Duration of Treatment

The randomized withdrawal study did demonstrate maintenance efficacy for Seroquel XR as monotherapy in MDD.

#### PREA Requirements

The sponsor will get a waiver for ages less than 7, and a deferral for ages 7-17 for the treatment of MDD.

### **5.1.3 Conclusions Regarding Efficacy Data**

The sponsor has, in my view, provided sufficient evidence to support claims for acute monotherapy, acute adjunctive therapy, and maintenance monotherapy for Seroquel XR in MDD.

## **5.2 Safety Data**

The safety review for these supplements was based on data from the 6 acute studies and the maintenance study. Overall, the safety findings for these supplements were consistent with the known adverse event profile for quetiapine and no important new adverse events that could be considered causally related to quetiapine were discovered as a result of the safety review. We are currently reviewing a comprehensive submission from the sponsor regarding metabolic effects of quetiapine. Both Drs. Levin and Hearst feel that the safety profile of Seroquel XR in MDD can be adequately characterized in labeling. I agree that the safety profile we are seeing in the MDD population is not different from the profile we have already observed in other populations. However, it is of some concern that approving these claims will likely greatly expand the use of this product. Thus, we need to think carefully about the risks and benefits of such expanded use, particularly with regard to longer-term risks which are not yet fully established. Tardive dyskinesia is an accepted risk in schizophrenic and bipolar patients, and in fact, thought to be somewhat reduced in association with atypical antipsychotic drugs, such as quetiapine. However, the sponsor has not addressed this concern. Furthermore, there is accumulating evidence that quetiapine may have substantial metabolic risks (weight gain, hyperlipidemia, and hyperglycemia) with all the attendant longer-term cardiovascular and other risks. Thus, if these new claims are to be approved, it will be important to ensure that labeling, and perhaps other educational material, fully informs prescribers and patients about these known and potential risks.

## **5.3 Clinical Sections of Labeling**

We have made a number of modifications to the sponsor's proposed labeling and asked them to make a number of additional modifications.

## **6.0 WORLD LITERATURE**

The sponsor apparently provided literature references but without any comment on methodology or any assessment of what they provided. Dr. Hearst simply stated: "There were no new significant findings in the literature." In the CR literature we have mentioned the published literature as one possible source of information of the longer-term risks associated with the use of this drug, e.g., tardive dyskinesia.

## **7.0 FOREIGN REGULATORY ACTIONS**

The reviewer does not comment on whether or not Seroquel XR is approved in any other countries for the treatment of MDD.

## **8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING**

We have not, as yet, taken this application to the PDAC.

## **9.0 DSI INSPECTIONS**

Inspections were conducted at three sites that enrolled patients from pivotal studies. The data from these sites were deemed to be acceptable.

## **10.0 LABELING AND APPROVAL LETTER**

Our proposal for labeling will be included in the CR letter.

## **11.0 CONCLUSIONS AND RECOMMENDATIONS**

The sponsor has submitted sufficient data to support the conclusion that Seroquel XR is effective as acute monotherapy and adjunctive therapy and as maintenance monotherapy in the treatment of MDD. The safety profile, to the extent that it can be characterized, appears to be similar to that observed with this drug in other conditions. However, there remains a concern about longer-term risks with this drug, in particular risks related to metabolic changes with this drug and the possibility of tardive dyskinesia. These issues become even more important as the distribution of this drug to a much broader patient population is considered. Thus, we will ask the sponsor to strengthen labeling, particularly with regard to the metabolic concerns, and gather whatever additional evidence might be available to address the concern about tardive dyskinesia. Thus, I will issue a Complete Response letter for these supplements.

cc:

Orig NDA 22-047S-010/011/012

HFD-130

HFD-130/TLaughren/MMathis/RLevin/EHearst/RGrewal

DOC: Laughren\_NDA22047\_S-010-011-012\_Seroquel XR\_CR Memo.doc

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/s/

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Thomas Laughren  
12/21/2008 04:13:39 PM  
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Clinical Team Leader Review Memo

<b>Date</b>	October 21, 2009
<b>From</b>	Robert L. Levin, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/Supp #</b>	22-047/(b) (4) S11 (b) (4)
<b>Proprietary/ Established</b>	Seroquel XR Seroquel XR extended-release
<b>Dosage forms/ strength</b>	50 mg, 200 mg, 300 mg extended-release tablets
<b>Proposed Indications</b>	(b) (4) adjunctive Therapy to Antidepressants for MDD in adults (b) (4)
<b>Recommended:</b>	(b) (4) approval for Adjunctive Therapy to Antidepressants in MDD (b) (4)

### 1. Introduction and Background

On February 27, 2008, the sponsor submitted 3 supplemental NDAs for quetiapine extended-release (Seroquel XR) in the treatment of Major Depressive Disorder for the following indications: 1) Seroquel XR monotherapy in the treatment of MDD (S-010); 2) Seroquel XR as adjunctive therapy to antidepressants in patients with MDD who have had a suboptimal response to antidepressants in the current episode (S-011); and 3) Seroquel XR monotherapy as maintenance treatment for MDD (S-012).

The studies demonstrated efficacy for each of the proposed indications. However, the Division took Complete Response actions (on December 22, 2008), due to concerns about specific safety risks including metabolic abnormalities (weight gain, hyperlipidemia, hyperglycemia/glucose dysregulation) and their associated serious cardiovascular and other risks. Tardive dyskinesia is a long-term risk that was also considered in taking the CR action. Another concern is the possibility that treatment with antipsychotics may be associated with an increased risk of sudden cardiac death. Thus, the Division requested that the sponsor submit data and analyses regarding these risks, in order to address the concerns.

The Division held a meeting of the Psychopharmacological Drugs Advisory Committee (PDAC), in order to have a thorough discussion of the complicated issues related to these applications. The PDAC meeting was held on April 8, 2009. The sponsor presented the efficacy and safety findings from supplements S10/S11/S12. In addition, they addressed the Division's concerns about metabolic abnormalities, tardive dyskinesia, and sudden cardiac death. The advisory committee concluded that the sponsor had demonstrated the efficacy of Seroquel XR in the MDD studies of short-term monotherapy, short-term adjunctive therapy, and maintenance monotherapy. Furthermore, the committee

recommended approval for the indication of adjunctive therapy to antidepressants in patients with a suboptimal response to antidepressant therapy, since these patients could represent a separate population with greater severity of disease and a need for different types of treatment than standard antidepressant monotherapy. Overall, the committee recommended against approving the supplements for short-term monotherapy and maintenance monotherapy, since the potential risks of treatment with Seroquel XR do not warrant the use of Seroquel XR as a first-line treatment of depression.

On June 2, 2009, the sponsor submitted a (b) (4) response, in order to address the safety concerns of the Division and the advisory committee. (b) (4)

(b) (4)  
the Division plans to take an approval action for Seroquel XR as adjunctive therapy to antidepressants in patients with MDD who have had a suboptimal response to standard antidepressant therapy.

#### **1. CMC**

There are no unresolved CMC issues for this application. There were no new data to review.

#### **2. Nonclinical Pharmacology/Toxicology**

There are no unresolved nonclinical pharmacology/toxicology issues for this application. There were no new data to review.

#### **3. Clinical Pharmacology/Biopharmaceutics**

There are no unresolved clinical pharmacology/biopharmaceutics issues for this application. There were no new data to review.

#### **4. Clinical and Statistical**

##### **4.1 Efficacy (Study description, dose selection, analysis, results)**

(b) (4)

#### 4.1.2 Adjunctive Therapy Studies

Both of the short-term (6-week) adjunctive therapy trials included fixed doses of 150 mg and 300 mg after a 2 to 4-day titration from 50 mg/day. There were no active comparators. Antidepressants used in the adjunctive trials were fluoxetine, sertraline, paroxetine, citalopram, escitalopram, venlafaxine, duloxetine, bupropion, and amitriptyline. Subjects included 939 males and females between the ages of 18 and 65 with a diagnosis of Major Depressive Disorder, single or recurrent episode, without psychotic features. Subjects must have been treated with an approved antidepressant in the current episode, and they must have had a suboptimal response, as demonstrated by having a HAM-D total score > 20. The ongoing antidepressant treatment was maintained at the same dose throughout the trials. There were 628 subjects treated with Seroquel XR, and 311 were treated with placebo. In both studies, subjects randomized to Seroquel XR treatment were treated with 50 mg/d for 2 days and then 150 mg/d for 2 days. In the 300 mg group, the dose was increased to 300 mg/d on Day 5.

There was evidence of a dose-response relationship. Both trials demonstrated efficacy for the 300 mg/day. Only one of the trials demonstrated efficacy for 150 mg/day (Study 7). In Study 6, the MADRS LS mean changes from baseline for placebo, 150 mg, and 300 mg were -11.7, -13.6, and -14.7, respectively). Thus, the Seroquel XR treatment effects were -1.9 and -3, respectively. Only the effect for 300 mg was statistically significant ( $p=0.008$ ). The effect was modest but in the range of antidepressant effects typically observed. For Study 7, the MADRS LS mean changes from baseline for placebo, 150 mg, and 300 mg were -12.21, -15.26, -14.94, respectively. The treatment effects for the 150 mg and 300 mg doses (3.1 and 2.7, respectively) were statistically significant and modest.

Phillip Dinh, Ph.D. conducted the statistical review, and he confirmed the sponsor's efficacy results for studies 6 and 7 described above. The primary endpoint was the change from randomization to Week 6 in the MADRS total score. Missing values were imputed by the LOCF method. The primary efficacy variable for both studies was analyzed by a mixed model ANCOVA with MADRS total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

The efficacy results for Study 6 and Study 7 are presented in the tables below (adapted by Dr. Ding from the sponsor's table).

**Table 27. Study D1448C00006: Sponsor's primary efficacy results: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg
Sample size	143	143	146
LS Means	-11.70	-13.60	-14.70
Difference from placebo (95% confidence interval)		-1.90 (-3.93, 0.14)	-2.99 (-5.02, -0.97)
Unadjusted p-values		0.067	0.004
Adjusted p-values		0.067	0.008

(Source: d1448c00006 Study Report; Table 21, page 106)

**Table 33. Study D1448C00007: Sponsor's primary efficacy results: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg
Sample size	160	166	161
LS Means	-12.21	-15.26	-14.94
Difference from placebo (95% confidence interval)		-3.05 (-4.92, -1.17)	-2.73 (-4.62, -0.84)
Unadjusted p-values		0.002	0.005
Adjusted p-values		0.003	0.005

(Source: d1448c00007 Study Report; Table 20, pages 98-99)

The key secondary efficacy variable in both studies was the change from randomization to Week 6 in the Q-LES-Q percent maximum total score. The key secondary analysis model was a mixed effect ANCOVA model with baseline Q-LES-Q percent maximum total score as a covariate, treatment as a fixed effect, and center as a random effect. Neither of the studies was positive on the secondary endpoint.

#### **4.1.3 Pediatric use/PREA waivers/deferrals**

The Agency has granted a waiver for the study of Seroquel XR in children less than 7 years of age with Major Depressive Disorder, due to the low prevalence of MDD in children younger than 7 years. The Agency has granted a deferral for the study of Seroquel XR in MDD in adolescents (ages 7 to 18).

The sponsor is in the process of fulfilling the Written Request through the conduct of a pediatric clinical development program. On February 11, 2003, the Division issued a Pediatric Written Request for Seroquel XR Tablets (NDA 20-639) for the treatment of schizophrenia and bipolar mania. The Division agreed (October 11, 2005) that one pharmacokinetic study comparing the XR and immediate-release (IR) formulations of Seroquel XR would satisfy the sponsor's pediatric study obligations for Seroquel XR, provided that the IR formulation is demonstrated to be efficacious in pediatric patients in the Pediatric Written Request program.

## **4.2 Safety Data**

### **4.2.2 General safety considerations**

The safety database was adequate for assessing the safety profile of Seroquel XR adjunctive treatment for the proposed indication. There was an adequate total exposure at the clinically relevant doses of Seroquel XR. Furthermore, the safety assessments were appropriate and adequate. There were no new or unexpected safety findings in the adjunctive studies, compared to the safety profile of quetiapine in other indications. Furthermore, the safety profile of quetiapine as adjunctive therapy to antidepressants was essentially identical to that in the quetiapine monotherapy MDD studies.

### **4.2.3 Safety findings from the clinical studies**

In the adjunctive acute studies, a total of 627 subjects were exposed to quetiapine XR for a total exposure of 63.2 person-years (32.8 for the 150 mg dose and 30.4 for the 300 mg dose). In the 4 short-term monotherapy studies, a total of 1149 subjects had a total quetiapine exposure of 123.6 person-years (17.7 for 50 mg, 66.0 for 150 mg, and 40.0 for 300 mg).

There were no deaths in the adjunctive therapy studies. There were few serious adverse events in either treatment group. One case of syncope was possibly related to treatment with quetiapine. Discontinuations due to adverse events were dose-related. For studies 6 and 7 combined, the proportions of subjects who discontinued due to an adverse event were 2%, 9%, and 15% in the placebo, 150 mg, and 300 mg groups, respectively. For the quetiapine groups combined, a total of 24% of subjects discontinued due to adverse events. Many of these adverse events were drug-related: somnolence, fatigue, and dizziness.

Extrapyramidal symptoms were dose-related. The proportions of subjects reporting EPS in the placebo, 150 mg, and 300 mg groups were 4.2%, 3.8%, and 6.4%, respectively. Akathisia and tremor accounted for most of the EPS reports in the quetiapine XR groups. None of the EPS were SAE. Discontinuations due to EPS were reported for subjects in the quetiapine XR groups and none in the placebo group.

Weight gain was dose-related. The proportions of subjects with weight gain >7% of body weight was 1.7% in the placebo group, 3.2% in the quetiapine 150 mg/day group, and 7.2% in the quetiapine 300 mg/day group.

### **4.2.4 Safety update**

Dr. Hearst reviewed the 4-month safety update. He concluded that there were no new or unexpected safety findings for treatment with Seroquel XR. I agree with his conclusion.

## **5 Psychopharmacological Drugs Advisory Committee (PDAC) Meeting**

Refer to the Introduction and Background section above for a discussion of the PDAC meeting.

## **6 Labeling**

The Division's proposed labeling for the adjunctive therapy claim will focus on the following sections: Indications, Dosing and Administration, Adverse Events, and Clinical Trials. Detailed labeling proposals will be contained in a separate label document.

## **7 Conclusions and Recommendations**

The studies demonstrated the efficacy of Seroquel XR in the treatment of Major Depressive Disorder in adults [REDACTED] (b) (4). Treatment with Seroquel XR was reasonably safe and well tolerated in the short-term studies and maintenance study. There were no new or unexpected adverse events or other safety findings, compared to the safety profile of treatment with Seroquel XR in other patient populations. However, long-term treatment with Seroquel XR poses several risks including metabolic abnormalities such as excessive weight gain, hyperlipidemia, and glucose dysregulation, and insulin resistance. Complications of such risks include serious cardiovascular disorders (hypertension, myocardial infarction) as well as cerebrovascular accidents and death. In addition, long-term treatment with atypical antipsychotics such as Seroquel XR carries the risk of tardive dyskinesia. Finally, some evidence suggests that treatment with antipsychotics potentially increases the risk of sudden cardiac death.

I recommend that the Division take an Approval action for supplement S-011: Seroquel XR for adjunctive therapy to antidepressants in patients with MDD who have had a suboptimal response to antidepressants. These patients likely represent a separate population with greater severity of disease and a need for different types of treatment than standard antidepressant monotherapy. Generally, the potential risks described above would be more acceptable in a population of patients with MDD who have not responded to standard antidepressant therapy.

(b) (4)

Cc: NDA/22-047

T Laughren  
M Mathis  
E Hearst  
J Touré

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Robert L. Levin, M.D., October 21, 2009  
Medical Officer, Division of Psychiatry Products

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

(b) (4)-----

NDA-22047

SUPPL-11

ASTRAZENECA  
PHARMACEUTICA  
LS LP

SEROQUEL XR

(b) (4)

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ROBERT L LEVIN

10/21/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA 22-047
Submission Number	S (b) (4) 011 (b) (4)
Submission Code	N
Established Name	quetiapine XR
Trade Name	Seroquel XR
Applicant	AstraZenica
Material Received	(b) (4) Response Letter and Safety Update

### I. Review

This response document addresses issues identified in the United States Food and Drug Administration (FDA) Complete Response Letter for the SEROQUEL extended-release (quetiapine XR) Major Depressive Disorder (MDD) supplements and incorporates feedback from the Psychopharmacologic Drugs Advisory Committee Meeting of 8 April 2009.

In the Complete Response Letter for MDD, the FDA stated that the efficacy of quetiapine XR in MDD had been demonstrated. In the Psychopharmacologic Drugs Advisory Committee (PDAC) meeting, it was concluded that quetiapine was acceptably safe as treatment for MDD in the adjunct setting but not as a broad-use monotherapy agent. The FDA raised concerns about longer-term metabolic risks and risk of tardive dyskinesia (TD) in an expanded patient population.

This response further characterizes data relating to metabolic changes, TD, and sudden cardiac death, and includes a benefit-risk assessment for lower doses of quetiapine XR (50 to 300 mg/day) for the treatment of MDD as adjunct therapy and as monotherapy.

(b) (4)

## Revised indication

To better define the population of patients that are candidates for quetiapine XR for MDD, AstraZeneca has proposed the following revised indication as part of this response.

### Major Depressive Disorder

SEROQUEL XR is indicated for

(b) (4) adjunct therapy to antidepressants.

(b) (4)

## Post-approval surveillance studies

AstraZeneca is committed to the post-approval evaluation of quetiapine XR treatment and evaluation of the potential longer-term metabolic risk (b) (4)

As stated in the FDA briefing materials for the PDAC meeting of 8 April 2009, the safety findings for the MDD studies were generally consistent with the known safety profile of quetiapine. This response addresses the longer-term risks for the treatment of MDD, focusing on the specific safety topics in the complete response letter, which included metabolic parameters, TD, and SCD.

## Sponsors Safety Data Analysis:

In this section, safety data have been pooled by the sponsor across different study types to allow a more comprehensive review of the specific topics. These data came from AstraZeneca-sponsored studies that had completed as of 31 December 2008. Data have been analyzed to explore the dose relationships, effects over time, and effects of treatment discontinuation. As agreed with the FDA, Pool D and Pool E include both MDD and GAD studies, because combining these indications provides a larger population for safety evaluation of non-psychotic patients receiving lower doses of quetiapine (50 to 300 mg/day), as opposed to the higher doses (up to 800 mg/day) used for other approved indications.

## Sponsor conclusions on potential metabolic risks in patients with MDD

*Within the MDD program, where lower daily doses are used (50 to 300 mg/day), the mean changes in metabolic variables appeared generally similar to, or smaller than, those seen in studies in indications using higher doses (up to 800 mg/day).*

*Within the overall clinical study program and the MDD studies, there was no evidence that quetiapine XR was associated with AEs potentially related to atherosclerotic cardiovascular disease. In addition, no signal was detected in a review of the AERS database.*

*Considering all of the available clinical study data, there was no consistent trend for increasing risk of AEs potentially related to diabetes with quetiapine. Within the MDD studies, there was no evidence that quetiapine XR was associated with AEs potentially related to diabetes. An increased number of AEs potentially related to diabetes was reported in the longer-term, randomized withdrawal studies, but not in the fixed-dose, placebo-controlled, short-term studies.*

*Evaluation of metabolic data from the MDD population did not reveal any metabolic findings or suggest potential longer-term metabolic risks inconsistent with those seen in the currently approved indications of schizophrenia and bipolar disorder.*

The current labeling for quetiapine and quetiapine XR contains warnings for hyperglycemia, diabetes, weight gain, and hyperlipidemia, for the higher dose indications of schizophrenia and bipolar disorder.

## **Sponsor Conclusions on tardive dyskinesia**

*While there exists a risk of TD with quetiapine, as indicated in the product labeling, this risk is low, as supported by the frequency of TD AEs associated with quetiapine in clinical studies across all indications (0.2%, 53/26454 patients).*

## **Sponsor Conclusions on sudden cardiac death**

*In a study using a retrospective analysis of a Medicaid database, Ray et al 2009 reported that current users of typical and atypical antipsychotic drugs, including quetiapine, had higher rates of SCD than did nonusers. His study suggested that patients exposed to lower doses of atypical antipsychotic drugs, including quetiapine, had a lower risk of SCD compared with users of higher doses. An evaluation of overall mortality, SCD (including a blinded adjudication by an external cardiologist), QT data, and AE terms indicating potential proarrhythmic effects from clinical trials and postmarketing databases was conducted.*

*These analyses did not identify a higher risk of SCD among patients treated with quetiapine.*

## **Postmarketing data**

A review of the AstraZeneca internal postmarketing database was undertaken using a search strategy that is provided. Among the more than (b) (4) patients with known exposure to quetiapine (XR or IR), 14596 cases matched the search criteria for diabetes-related events, 1177 cases matched the search criteria for changes in lipids, and 2271 cases matched the search criteria for weight gain. Most cases were confounded by concomitant or prior medication, comorbid risk factors, and/or an alternative cause, or they contained incomplete information regarding medical history; concomitant drugs; the course, treatment, or outcome of the events; and/or the relationships of these events to quetiapine or quetiapine XR.

Published studies that specifically identify diabetes as the outcome and provide a formal statistical comparison between quetiapine and either conventional antipsychotics or no antipsychotic exposure were reviewed by the sponsor.

Four studies compared quetiapine use to a general population. Three studies (Buse et al 2003, Feldman et al 2004, Sacchetti et al 2005) showed overall increased risk compared to a general population with no antipsychotic exposure and no psychiatric disorders; however, this increased risk could be due, at least in part, to an increased risk of developing diabetes in those with psychiatric disorders in general. One study (Barnett et al 2006) found no increased risk for patients prescribed quetiapine versus patients prescribed corticosteroids or proton pump inhibitors.

Three studies attempted to account for the possible general increased risk for diabetes with psychiatric disorders by comparing quetiapine users with patients with psychiatric diagnoses who were not treated with antipsychotics or who had not been treated for extended periods of time. One study found no increased risk for quetiapine, despite the quetiapine users having a higher prevalence of diabetic risk factors (Gianfrancesco et al 2003). The other two assessed the effect of varying definitions of diabetes and antipsychotic use on the association. Both showed that less robust analyses found increased risk, while the more robust analyses found no increased risk for quetiapine use compared with no antipsychotic exposure in patients with psychoses (Gianfrancesco et al 2006a, Gianfrancesco et al 2006b).

Five studies showed increased risk for quetiapine relative to conventional antipsychotic exposure (Citrome et al 2004, Guo et al 2006, Guo et al 2007, Lambert et al 2006a, Sernyak et al 2002). However, in 2 of the studies, the association held only in subgroups: men (Citrome et al 2004) or younger patients (Sernyak et al 2002).

Ten studies found no increased risk for quetiapine compared to conventional antipsychotics, including the 4 studies described above that also compared quetiapine to a general population: 3 that found increased (Buse et al 2003, Feldman et al 2004, Sacchetti et al 2005) and 1 that found no increased risk

(Barnett et al 2006). Additional studies showing no increased risk compared to use of conventional antipsychotics required that patients be on monotherapy only, reducing the potential for inappropriate attribution of an outcome to one or another antipsychotic (Lambert et al 2005, Lambert et al 2006b, Leslie and Rosenheck 2004, Miller EA et al 2005), a strength compared to studies that did not require monotherapy (Barner et al 2004, Yood et al 2008).

At least 3 studies suggest that physicians may be “channeling” patients with pre-existing diabetes or at higher risk of developing diabetes to quetiapine (Gianfrancesco et al 2006a, Lamberti et al 2004, Leslie and Rosenheck 2005).

## **Safety Update**

As required by the Food and Drug Administration (FDA) Complete Response Letter dated 22 December 2008 for the SEROQUEL XR (quetiapine fumarate extended-release, hereafter referred to as quetiapine XR) major depressive disorder (MDD) supplemental New Drug Applications (NDA 22-047, S-010/S-011/S-012), AstraZeneca hereby submits a safety update as described by CFR 314.50(d)(5)(vi)(b). Reference is made to the 4-month safety update for these supplements that was submitted on 25 June 2008. As communicated via e-mail correspondence on 15 April 2009, this safety update for MDD includes safety information from a recently completed study 16 generalized anxiety disorder (GAD) study and limited information from an ongoing MDD study. In addition, a world literature search conducted for SEROQUEL and safety information for the period of January 2007 through April 2009 is provided.

## **Study 16**

### **Exposure:**

A total of 409 subjects were randomized 1:1 in adjunct Study 16, 200 to the placebo group and 209 to the quetiapine XR group. No patients were excluded from the safety analysis set. At the time of data collection cut-off for the filing of this safety update (6 May 2009), 397 patients were randomized in Study 44. Data for 134 patients were included in the study database at the time of the data cut-off.

**Table 4** Derivation of safety analysis set (Study 16)

	PLA N=200	QTP XR N=209
Excluded from safety analysis set	0	0
Not treated	0	0
Safety analysis set	200	209
Excluded from MITT analysis set	2	5
No valid baseline or post-baseline HAM-A score	2	5
MITT analysis set	198	204
Excluded from PP analysis set	21	23
PP analysis set	177	181
TDSS analysis set	159	141

HAM-A Hamilton Rating Scale for Anxiety; MITT Modified intention-to-treat; N Number of patients in treatment group; PP Per protocol; PLA Placebo; QTP XR Quetiapine extended-release; TDSS Treatment discontinuation signs and symptoms.

Overall, the discontinuation rate during the study period was higher in the quetiapine XR group (27.3%) than in the placebo group (16.0%). Adverse events were the main reason for discontinuation in the quetiapine XR group (12.0% of patients; compared to 2.0% of patients treated with placebo). Lost to follow up was the main reason for discontinuation in the placebo group (7.0%, similar to 5.3% for the quetiapine XR group). There were no (0.0%) discontinuations due to lack of therapeutic response in patients treated with quetiapine XR, and only 1 (0.5%) in placebo-treated patients.

Of the 409 patients assigned to randomized treatment, all received double-blind treatment with study medication. The mean overall exposure, in terms of days of double-blind treatment, was similar between the treatment groups (52.4 days for patients receiving placebo and 48.8 days for patients receiving quetiapine XR). Total exposure in patient-years was also similar between the 2 groups (28.70 patient-years and 27.95 patient-years for those receiving placebo and quetiapine XR, respectively).

The treatment groups were generally well-balanced with respect to demographic characteristics. Of the 402 patients included in the MITT analysis set, 106 (26.4%) were men and 296 (73.6%) were women. The distribution of patients by sex was similar in the quetiapine XR and placebo groups, and Caucasian and Black patients comprised the largest groups in the MITT analysis set.

The treatment groups were generally well balanced between the placebo and quetiapine XR groups with regard to baseline psychiatric characteristics and history. The baseline disease characteristics of the safety analysis set were similar to those of the MITT analysis set.

Concomitant use of SSRIs was common among patients in both the placebo (73.5%) and quetiapine XR (76.6%) groups, and use of individual SSRIs was

similar between both groups. Concomitant use of SNRIs was infrequent, with 27.5% of placebo patients and 26.3% of quetiapine XR patients using this class of drugs. The most common anxiolytics used as concomitant therapy in both the placebo and quetiapine XR groups were escitalopram hydrochloride and paroxetine hydrochloride. Use of SSRIs and SNRIs in both treatment groups was well balanced.

**Table 13** Patients who had an adverse event in any category, safety analysis set (Study 16)

Category of adverse event	PLA N=200 n (%)	QTP XR N=209 n (%)
Any adverse event	120 (60.0)	154 (73.7)
Serious adverse event	0	0
Serious adverse event leading to death	0	0
Serious adverse event not leading to death	0	0
Drug-related adverse event <sup>1</sup>	72 (36.0)	130 (62.2)
Adverse events leading to discontinuation	4 (2.0)	24 (11.5)

<sup>1</sup> As judged by the Investigator.

Note: All AEs occurred from start of study treatment to last dose plus 30 days.

Note: Patients with multiple events in the same category are counted only once.

Note: Percentages are calculated as  $n/N \times 100$ .

N Number of patients in treatment group; n Number of patients; PLA Placebo; QTP XR Quetiapine extended-release.

**Table 15 Common ( $\geq 2\%$ ) adverse events by preferred term, safety analysis set (Study 16)**

Adverse event <sup>a</sup>	PLA	QTP XR
	N=200	N=209
	n (%)	n (%)
Dry mouth	16 (8.0)	49 (23.4)
Somnolence	24 (12.0)	47 (22.5)
Sedation	5 (2.5)	26 (12.4)
Headache	21 (10.5)	24 (11.5)
Dizziness	9 (4.5)	22 (10.5)
Fatigue	8 (4.0)	20 (9.6)
Insomnia	3 (1.5)	15 (7.2)
Constipation	8 (4.0)	13 (6.2)
Nausea	12 (6.0)	12 (5.7)
Increased appetite	1 (0.5)	8 (3.8)
Upper respiratory tract infection	5 (2.5)	8 (3.8)
Weight increased	2 (1.0)	8 (3.8)
Nasopharyngitis	17 (8.5)	7 (3.3)
Abnormal dreams	2 (1.0)	6 (2.9)
Diarrhoea	6 (3.0)	6 (2.9)
Dyspepsia	3 (1.5)	6 (2.9)
Libido decreased	0 (0.0)	5 (2.4)
Paraesthesia	1 (0.5)	5 (2.4)

<sup>a</sup> Patients with multiple events falling under the same preferred term are counted only once in that term.

Note: Common adverse event is defined as an event occurring at an incidence of  $\geq 2\%$  in any treatment group.

Note: Events sorted by decreasing frequency in the QTP XR treatment group.

Note: Percentages are calculated as  $n/N \times 100$ .

MedDRA Medical Dictionary of Regulatory Activities; N Number of patients in treatment group; n Number of patients; PLA Placebo; QTP XR Quetiapine extended-release.

Discontinuations due to AEs in Study 16 occurred in 4 (2%) patients receiving placebo and in 23 (11%) patients receiving quetiapine XR during the study. One patient discontinued study participation due to an AE in the placebo lead-in period, and 1 patient discontinued study participation after the treatment period.

Nervous system disorders represented the largest proportion of AEs leading to discontinuation (18 patients, 8.6%) in the quetiapine XR group, with sedation being the most frequently reported (11 patients, 5.3%). Of the AEs that led to discontinuation, nearly all started within the first 9 days of study treatment.

In Study 16, the percentage of patients whose SAS total score worsened between baseline and the end of treatment was 6.7% for the placebo group and 11.2% for the quetiapine XR group.

The majority of patients in each group had no change in their SAS total score from baseline to end of treatment (75.6% and 79.5% for placebo and quetiapine

XR, respectively). The incidence of AEs potentially related to EPS was 2.0% in the placebo group and 3.8% in the quetiapine XR group. All of these potentially EPS-related AEs were of mild or moderate severity, and there were no SAEs. One of the events resulted in the patient discontinuing from the study (event of moderate restlessness on 150 mg quetiapine XR). Most of the events were considered by the Investigator to be related to study medication.

The percentage of patients whose BARS global assessment score worsened between baseline and end of treatment was 3.6% for the placebo group and 4.9% for the quetiapine XR group. The majority of patients in each group had no change in their BARS global assessment score from baseline to end of treatment (84% and 87.8% for placebo and quetiapine XR, respectively).

**Table 18** Adverse events potentially related to EPS, safety analysis set (Study 16)

	PLA N=200	QTP XR N=209
MedDRA preferred term <sup>a</sup>	n (%)	n (%)
Total	4 (2.0)	8 (3.8)
Akathisia	1 (0.5)	0 (0.0)
Psychomotor hyperactivity	1 (0.5)	2 (1.0)
Restlessness	1 (0.5)	3 (1.4)
Tremor	1 (0.5)	3 (1.4)

<sup>a</sup> Patients with multiple events falling under the same preferred term are counted only once in that term.

Note: All AEs occurred from start of study treatment to last dose plus 30 days.

Note: Events presented by decreasing frequency in the QTP XR treatment group.

Note: Percentages are calculated as  $n/N \times 100$ .

EPS Extrapyramidal symptoms; MedDRA Medical Dictionary for Regulatory Activities; N Number of patients in treatment group; n Number of patients; PLA Placebo; QTP XR Quetiapine extended-release.

No instances of TD or potentially associated events were reported in Study 16 or Study 44 (as of 6 May 2009).

### Study 16- Metabolic change

The small hemodynamic changes and the weight gains in the quetiapine XR group were consistent with the anticipated effects based on the pharmacological profile of quetiapine. Mean changes in glucose from baseline to Week 8 were minimal: 0.85 mg/dL (15.54 mg/dL) for the quetiapine XR group and 1.70 mg/dL (16.01 mg/dL) for the placebo group. Shifts from non-clinically important values at baseline to clinically important values in glucose (high) at any time (fasting status confirmed) occurred in 10/152 (6.6%) patients in the placebo group and in 5/161 (3.1%) patients in the quetiapine XR group. One of 176 (0.6%) patients in the placebo group had a shift from non-clinically important HbA1c at baseline to clinically important (high) at any time during the study. There were no other clinically important shifts in other glucose regulation parameters during the study.

Triglycerides exhibited a mean increase from baseline for the quetiapine XR patients (5.81 mg/dL) and a mean decrease from baseline for the patients in the placebo group (-8.73 mg/dL). In addition, there were small decreases in total cholesterol and LDL cholesterol levels in both treatment groups. Notably, there was a high degree of inter-patient variability in the changes from randomization to Week 8 in lipid and glucose regulation parameters (glucose and insulin).

The percentage of patients with a weight gain of  $\geq 7\%$  was higher in the quetiapine XR group than in the placebo group, but was generally low (9 patients [4.3%] in the quetiapine XR group and 2 patients [1.0%] in the placebo group). In both treatment groups there was a trend for a weight gain of  $\geq 7\%$  to occur more frequently in patients in the lower 2 BMI categories (18.5 kg/m<sup>2</sup> to <25 kg/m<sup>2</sup>, and 25 kg/m<sup>2</sup> to <30 kg/m<sup>2</sup>).

The overall incidence of patients with a treatment-emergent shift from <3 to  $\geq 3$  metabolic risk factors was higher in the quetiapine XR group (14.3%) compared with the placebo group (7.8%).

The incidence of AEs potentially related to diabetes mellitus was low (4 patients, 1.0%). The total incidence of AEs of this type was equal between the placebo and the quetiapine XR groups.

Overall, the results of Study 16 with respect to metabolic risk factors were consistent with those observed in GAD program according to the sponsor.

## **WORLD LITERATURE SEARCH**

A world literature search has been conducted for Seroquel and safety information for the period of January 2007 through April 2009. Eight hundred and twenty six records were retrieved from the following databases using the strategy below.

Search Strategy (826 hits):

1. safety.mp 1106021
2. (seroquel or quetiapine).title,abstract. 17984
3. 1 and 2 3348
4. limit 3 to yr="2007 -Current" 1175
5. remove duplicates from 4 826

Database: EMBASE & BIOSIS Previews & Journals@Ovid & Current Contents & Planet & Ovid MEDLINE(R) & Your Journals@Ovid & IPAB.

Additional searches were performed for Seroquel as it relates to Major

Depressive Disorder for the period of May 2007 through April 2009.

Search Strategy (Literature 97 hits):

1. ((Seroquel or quetiapine) adj3 ((sustained or extended or prolonged) adj release)).mp.
2. ((Seroquel or quetiapine) adj (XR or ER or XL or SR)).mp.
3. 1 or 2
4. limit 3 to yr="2007 -Current"

Strategy (Press Releases 10 hits):

1. Source: Reuters - search for Seroquel XR (included 10 unique, relevant releases for 2007-April 2009) Strategy (Press Releases 40 hits):
  1. Source: Trial Trove quetiapine fumarate SR fields above: 2007 or 2008 or 2009 Database: EMBASE & BIOSIS Previews & Journals@Ovid & Current Contents & Planet & Ovid MEDLINE(R) & Your Journals@Ovid & IPAB.

The literature review which relied on 973 abstracts, including 3 full text documents. This literature review did not reveal any new or important findings regarding Seroquel XR. No new safety signals or findings were identified, and no missing items were identified. I have reviewed this search and agree with the sponsor's findings.

### **Key Safety Sponsor Findings**

The adverse event (AE) profile, clinical laboratory evaluations, vital signs, and other observations related to safety in Study 16 were consistent with previous investigations of quetiapine XR in the treatment of GAD. No new safety concerns were revealed during treatment with quetiapine XR. The following list contains safety findings of particular interest in Study 16:

There were no deaths or serious AEs in this study.

There was 1 AE potentially related to neutropenia/agranulocytosis (quetiapine XR group). There were no AEs potentially related to suicidality. In the quetiapine XR group 6 (2.9%) of patients experienced AEs potentially related to sexual dysfunction, while none of the patients in the placebo group experienced such AEs.

No cases of sudden cardiac death or potentially associated events were reported. One AE of mild QT prolongation was reported in the quetiapine XR group.

A higher proportion of AEs potentially related to extrapyramidal symptoms was observed for quetiapine XR-treated patients compared to placebo-treated patients. The symptoms were mild to moderate in intensity and seldom led to discontinuation. No instances of tardive dyskinesia or potentially associated events were reported.

The small hemodynamic changes and the weight gain seen in the quetiapine XR group were consistent with the anticipated effects based on the pharmacological profile of quetiapine. The incidence of AEs potentially related to diabetes mellitus was low, and equal in the placebo and quetiapine XR groups.

Since Study 44 is ongoing, detailed analyses have not yet been performed for this study.

## **II. Recommendations:**

I am in agreement with the sponsor's findings that the Safety update does not change the overall safety profile to any significant extent.

(b) (4)

I agree with the PDAC's recommendations that Seroquel SR be approved for adjunctive use in MDD (b) (4)

Earl Hearst, M. D.  
HFD-130

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22047	----- [REDACTED] (b) (4)	-----	----- SEROQUEL XR

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EARL D HEARST  
08/10/2009

ROBERT L LEVIN  
08/10/2009

## CLINICAL REVIEW

Application Type NDA 22-047  
Submission Number S-010,011,012  
Submission Code N

Letter Date Feb 27, 2008  
Stamp Date Feb 27, 2008  
PDUFA Goal Date Dec 27, 2008

Reviewer Name Earl D. Hearst  
Review Completion Date 10/31/2008

Established Name quetiapine XR  
(Proposed) Trade Name Seroquel XR  
Therapeutic Class Atypical Antipsychotic  
Applicant AstraZenica

Priority Designation S

Formulation Extended Release Tablets  
Dosing Regimen 50 to 300 mg daily  
Indication Short-term monotherapy, adjunct  
use and monotherapeutic  
maintenance in MDD  
Intended Population Adults

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## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

I recommend all three supplements S-010, 011 and 012 be approved.

### **1.2 Recommendation on Postmarketing Actions**

There are no recommendations for actions other than the usual procedures.

#### **1.2.1 Risk Management Activity**

There are no recommendations for actions other than the usual procedures.

#### **1.2.2 Required Phase 4 Commitments**

AstraZeneca is currently working to fulfill the Written Request through the conduct of a pediatric clinical development program. On February 11, 2003, the Division issued a Pediatric Written Request for SEROQUEL Tablets (NDA 20-639) for the treatment of schizophrenia and bipolar mania. The Division agreed (October 11, 2005) that one pharmacokinetic study comparing the XR and immediate-release (IR) formulations of quetiapine will satisfy AstraZeneca's pediatric study obligations for SEROQUEL XR, provided that the IR formulation is demonstrated to be efficacious in pediatric patients in the Pediatric Written Request program.

#### **1.2.3 Other Phase 4 Requests**

None.

### **1.3 Summary of Clinical Findings**

#### **1.3.1 Brief Overview of Clinical Program**

The quetiapine XR MDD studies supporting the current registration package consists of the following three supplements S-010, 011 and 012:

Short-term Monotherapy: Studies 1, 2, 3 and 4

Short-term adjunct treatment: Studies 6 and 7

Maintenance treatment: Study 5

### 1.3.2 Efficacy

Quetiapine XR at doses of 50 mg/day, 150 mg/day, and 300 mg/day was superior to placebo as monotherapy in reducing the level of depressive symptoms through Week 6 or 8 in patients with MDD, as assessed by evaluation of Montgomery-Åsberg Depression Rating Scale (MADRS) total score in studies 1, 2 and 3. Study 4 was not significant..

Quetiapine XR at doses of 150 mg/day and 300 mg/day as adjunct to an antidepressant was superior to antidepressant therapy as adjunct to placebo in reducing the level of depressive symptoms at Week 6 in patients with MDD who had an inadequate response to previous antidepressant treatment, as assessed by evaluation of MADRS total score. See studies 6 and 7.

Maintenance treatment with quetiapine XR at flexible doses of 50 mg/day, 150 mg/day, or 300 mg/day statistically significantly increased the time to a depressed event in patients with MDD.

### 1.3.3 Safety

The safety data in this submission are generally consistent with current labeling for Seroquel SR. No new safety issues have been identified.

### 1.3.4 Dosing Regimen and Administration

The studies in this submission used SEROQUEL XR at doses of 50 mg, 150 mg, and 300 mg once daily. The sponsor recommends dosing as follows in their draft label.

Initial dosing should begin at 50 mg on Days 1 and 2, and be increased to 150 mg on Days 3 and 4. On Day 5 and onwards, if necessary, adjustments can be made upwards or downwards within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient.

For maintenance therapy in major depressive disorder the effective dose during initial treatment should be continued. The dose can be adjusted within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient.

### 1.3.5 Drug-Drug Interactions

There was no evidence from the SAE reports that quetiapine XR interacted with other medications during the acute monotherapy, acute adjunct therapy, and maintenance studies. Adjunct therapy with quetiapine XR at doses of 150mg/day or 300mg/day did not appear to have a consistent overall effect on the plasma concentrations of any of the adjunct antidepressants and their metabolites.

### 1.3.6 Special Populations

Safety in special groups defined by sex, age and race was explored by tabulating adverse event incidence by those factors. The incidence of common AEs in patients was generally consistent across gender, age from 18 to 65 and race in both monotherapy and adjunct treatment trials, and did not give rise to any new safety issues regarding the use of quetiapine XR in special groups and situations.

## **2 INTRODUCTION AND BACKGROUND**

### **2.1 Product Information**

Approval is being sought for the use of quetiapine extended release (XR) for 3 supplements, S-010, 011 and 012, short-term monotherapy, adjunct use and monotherapeutic maintenance in MDD.

### **2.2 Currently Available Treatment for Indications**

There are a number of approved products for these indications.

### **2.3 Availability of Proposed Active Ingredient in the United States**

This is an available approved drug.

### **2.4 Important Issues With Pharmacologically Related Products**

None to report.

### **2.5 Presubmission Regulatory Activity**

Key agreements between FDA and AstraZeneca were as follows:

Approval for both the monotherapy and adjunct indications could be based on a single positive monotherapy and a single positive adjunct study.

Approval for both the short-term monotherapy and maintenance indications could be based upon a single positive short-term monotherapy and a single positive maintenance therapy study.

Data on elderly patients were not required for approval of the MDD sNDA.

The results of a Columbia University-type analysis of suicidality should be provided.

### **2.6 Other Relevant Background Information**

n/a

### **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

#### **3.1 CMC (and Product Microbiology, if Applicable)**

n/a

#### **3.2 Animal Pharmacology/Toxicology**

The new nonclinical information reported in this sNDA involves the results of *in vitro* receptor binding studies comparing the binding properties of quetiapine with those of norquetiapine. *In vitro* functional assays were also conducted to characterize agonist or antagonist activity of quetiapine and norquetiapine at selected pharmacological targets. In all other respects the nonclinical data provided in NDA 20-639 are hereby cross-referenced to this sNDA. In addition, the nonclinical data provided in IND 74,629 are hereby cross-referenced to this sNDA.

### **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

#### **4.1 Sources of Clinical Data**

The quetiapine XR MDD studies supporting the current registration package consists of the following three supplements, S-010, 011 and 012.

Short-term Monotherapy: Studies 1, 2, 3 and 4

Short-term adjunct treatment: Studies 6 and 7

Maintenance treatment: Study 5

The data is presented in the EDR at

<\\CDSESUB1\EVSPROD\NDA022047\022047.enx>

#### **4.2 Tables of Clinical Studies**

The quetiapine XR clinical development program for MDD consists of 8 studies, as shown in [Table O 1](#).

**Table O 1 Summary of MDD Clinical Development Program**

Study number	Study type /	Treatment arms	Duration of treatment
D1448C00001 (Study 1)	Fixed Dose Monotherapy	-Quetiapine XR 50 mg -Quetiapine XR 150 mg -Quetiapine XR 300 mg -Placebo	6 wks
D1448C00002 (Study 2)	Fixed Dose Monotherapy	-Quetiapine XR 150 mg -Quetiapine XR 300 mg -Duloxetine 60 mg -Placebo	6 wks
D1448C00003 (Study 3)	Modified Fixed Dose Monotherapy	-Quetiapine XR 150/300 mg -Placebo	8 wks
D1448C00004 (Study 4)	Modified Fixed Dose Monotherapy	-Quetiapine XR 150/300 mg -Escitalopram 10/20 mg -Placebo	8 wks
D1448C00005 (Study 5)	Maintenance Treatment	-Quetiapine XR 50-300 mg -Placebo	4-8 wks open-label run-in treatment/ at least 16 wks open-label stabilization treatment/ up to 52 wks of randomized treatment
D1448C00006 (Study 6)	Adjunct treatment in inadequate responders	-Quetiapine XR 150, 300 mg -Placebo	6 wks
D1448C00007 (Study 7)	Adjunct treatment in inadequate responders	-Quetiapine XR 150, 300 mg -Placebo	6 wks
D1448C00014 <sup>a</sup> (Study 14)	Flexible Dose Monotherapy Elderly Patients	-Quetiapine XR 50-300 mg -Placebo	9 wks

<sup>a</sup> Study D1448C00014 was ongoing at the time databases were locked for this application.

### 4.3 Review Strategy

The review will center on the seven primary studies that support the three indications.

### 4.4 Data Quality and Integrity

The conduct of the studies in this program appears to be appropriate. No events were noted by the sponsor or reviewers that call into question the data obtained. The DSI review has not yet been received.

### 4.5 Compliance with Good Clinical Practices

AstraZeneca procedures, internal quality control measures and audit programs provide reassurance that the clinical study program was carried out in accordance with the ethical principles and standards that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice.

## **4.6 Financial Disclosures**

I have reviewed the financial disclosure information for the seven studies. There are a few investigators who have received more than \$25,000 in fees but the sponsor feels due to the low number of subjects at their sites that no bias overall in the studies would be present. I agree with this.

## **5 CLINICAL PHARMACOLOGY**

Clinical pharmacology findings for quetiapine IR have been described in the original registration dossier and supplemented with the extension of that registration for treatment of acute mania in bipolar disorder and for depressive episodes in bipolar disorder that were subsequently approved (NDA 20-639). Findings for quetiapine XR were described in the dossier for treatment of schizophrenia (NDA 22-047). Additional material is provided regarding 2 issues of pharmacokinetic and pharmacodynamic importance. The first question addressed the potential for pharmacokinetic interaction between quetiapine or its metabolites with various antidepressants and their metabolites. Pooled analysis from Studies 6 and 7 showed that blood concentrations of known antidepressants and their metabolites were not meaningfully altered following administration of quetiapine XR for up to 2 weeks. These results were concordant with the sponsor's review of the literature that revealed little propensity for meaningful interaction via known metabolic pathways. Review of the AstraZeneca post-marketing surveillance database did not reveal any significant concerns regarding potential interactions between quetiapine and antidepressant medications that are not already contained in the quetiapine professional information brochure.

## **6 INTEGRATED REVIEW OF EFFICACY**

### **6.1 Indication**

Approval is being sought for the use of quetiapine extended release (XR) for the treatment of major depressive disorder (MDD). This application contains data that supports quetiapine XR in the treatment of major depressive disorder as:

Monotherapy or adjunct therapy to other antidepressants

Maintenance of antidepressant effect

#### **6.1.1 Methods**

There were 7 Phase III studies on the safety and efficacy of quetiapine XR when used in the treatment of patients with Major Depressive Disorder (MDD). Studies 1 to 4 were acute monotherapy studies, Studies 6 and 7 were acute adjunct therapy studies (with ongoing antidepressant therapy), and Study 5 was a monotherapy maintenance treatment study.

## 6.1.2 General Discussion of Endpoints

In short-term Studies 1, 2, 3, 4, 6 and 7 the primary outcome variable was the change from baseline in the MADRS score. All statistical comparisons for quetiapine XR vs placebo for the two outcome variables were alpha-protected.

## 6.1.3 Study Design

All of the trials were placebo-controlled and two of the trials (Studies 2 and 4) employed active comparators. The active comparators (duloxetine 60 mg daily in Study 2; escitalopram 10-20 mg daily in Study 4) were both standard-of-care treatments for MDD and dosed at standard, known-to-be-effective doses.

In Studies 1 and 2, treatment duration was 6 weeks. In Studies 3 and 4, treatment duration was 8 weeks to allow for assessment of inadequate response after 2 weeks of treatment and a contingent increase in dose. In all 4 studies, the active treatment period was followed by a 2-week period of assessment of withdrawal signs and symptoms following treatment discontinuation via AE reports and the TDSS scale in patients who finished the 6- or 8-week treatment period. The 8- to 10-week duration of placebo treatment was justified by the value of tracking possible withdrawal symptoms in the quetiapine XR-treated patients and the close monitoring of all patients during both the treatment and the post-treatment periods.

The design of Study 5 allowed for a total quetiapine exposure of up to 78 weeks. Patients who responded to open-label treatment in 4 to 8 weeks were admitted to a 12- to 18-week stabilization treatment period. Those maintaining response during the stabilization period were then randomly assigned to continue with quetiapine XR or to switch to placebo treatment for up to 52 weeks. Analysis of time to a depressed event and proportions of patients experiencing such an event were in accord with current scientific and regulatory standards.

### **Key inclusion criteria (Studies 1, 2, 3, 4, 6, and 7)**

The key inclusion criteria for enrollment were as follows:

1. Male and female patients aged 18 to 65 years old, inclusive.
2. Documented clinical diagnosis meeting the DSM-IV criteria for any of the following:  
  
296.2x Major Depressive Disorder, Single Episode, or  
  
296.3x Major Depressive Disorder, Recurrent, as confirmed by MINI
3. HAM-D (17-item) total score and HAM-D Item 1 (depressed mood) score of:

Acute monotherapy studies (Studies 1, 2, 3, and 4): HAM-D total score  $\geq 22$ ,

HAM-D Item 1 score  $\geq 2$  at enrolment and randomization

Acute adjunct therapy studies (Studies 6 and 7): HAM-D total score  $\geq 20$ ,  
HAM-D Item 1 score  $\geq 2$  at enrolment and randomization

Maintenance treatment study (Study 5): HAM-D total score  $\geq 20$ , HAM-D Item  
1 score  $\geq 2$  at enrolment

4. Outpatient status at enrollment

Quetiapine XR was taken once daily at bedtime in all studies.

#### **Titration schedule for the acute treatment studies (Studies 1,2, 3, 4, 6, and 7)**

To maximize tolerability, quetiapine XR was gradually titrated from 50 mg to the final dose. In all studies, patients randomized to quetiapine XR treatment were administered a 50 mg dose for 2 days, with the dose being increased to 150 mg over the next 2 days for the 150 mg/day and 300 mg/day groups, and 300 mg thereafter in the relevant groups.

#### **Concomitant medication for all trials**

In all trials, concomitant psychotropic drug use was prohibited with the exception of sleep medications which were permitted only if the patient had been using the agent nightly for 28 days prior to enrollment. Any medication that would induce or inhibit the hepatic metabolizing cytochrome 3A4 enzymes was prohibited during and two weeks before the treatment period.

#### **Adjunctive Studies Medications**

The following antidepressants were allowed: amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine (Studies 6 and 7 only)

In the adjunct treatment trials (Studies 6 and 7), quetiapine XR or placebo treatment was randomly assigned to patients who had been treated with an approved antidepressant but who still exhibited HAM-D total scores of  $\geq 20$ , with Item 1 of the scale  $\geq 2$ . Blood samples were taken before the initiation of quetiapine XR treatment and at 2 and 4 weeks after in order to assess any changes in trough antidepressant plasma concentrations consequent to quetiapine exposure. Antidepressants on entry were restricted to amitriptyline, bupropion,

## **Individual Studies**

## **STUDY 1**

### **A Multicenter, Double-blind, Randomized, Parallel-group, Placebocontrolled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended-release (SEROQUEL®) as Monotherapy in the Treatment of Patients with Major Depressive Disorder (Moonstone Study)**

#### **International co-ordinating investigator**

Richard Weisler, MD

This study was conducted at 47 centers in the United States.

#### **Study design**

This was a 8-week, multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled Phase III study of the efficacy and safety of quetiapine XR 50 mg/day, 150 mg ( $3 \times 50$  mg) per day, and 300 mg/day as monotherapy in the treatment of patients with MDD. This study consisted of an up to 28-day enrollment period, a 6-week randomized treatment period with 1 of 4 treatment regimens (quetiapine XR 50 mg, quetiapine XR 150 mg, quetiapine XR 300 mg, or placebo), and a 2-week post-treatment period.

#### **Target population and sample size**

Male and female patients, 18 to 65 years old inclusive, with documented clinical diagnosis using the Mini-International Neuropsychiatric Interview (MINI) and meeting the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV) of either 296.2x Major Depressive Disorder, Single Episode, or 296.3x Major Depressive Disorder, Recurrent. The patients had to have a Hamilton Rating Scale for Depression (HAM-D) score  $\geq 22$  to be eligible for the study. The aim of this study was to randomize a patient population with approximately 40% of the patients having a HAM-D score of  $\geq 28$ .

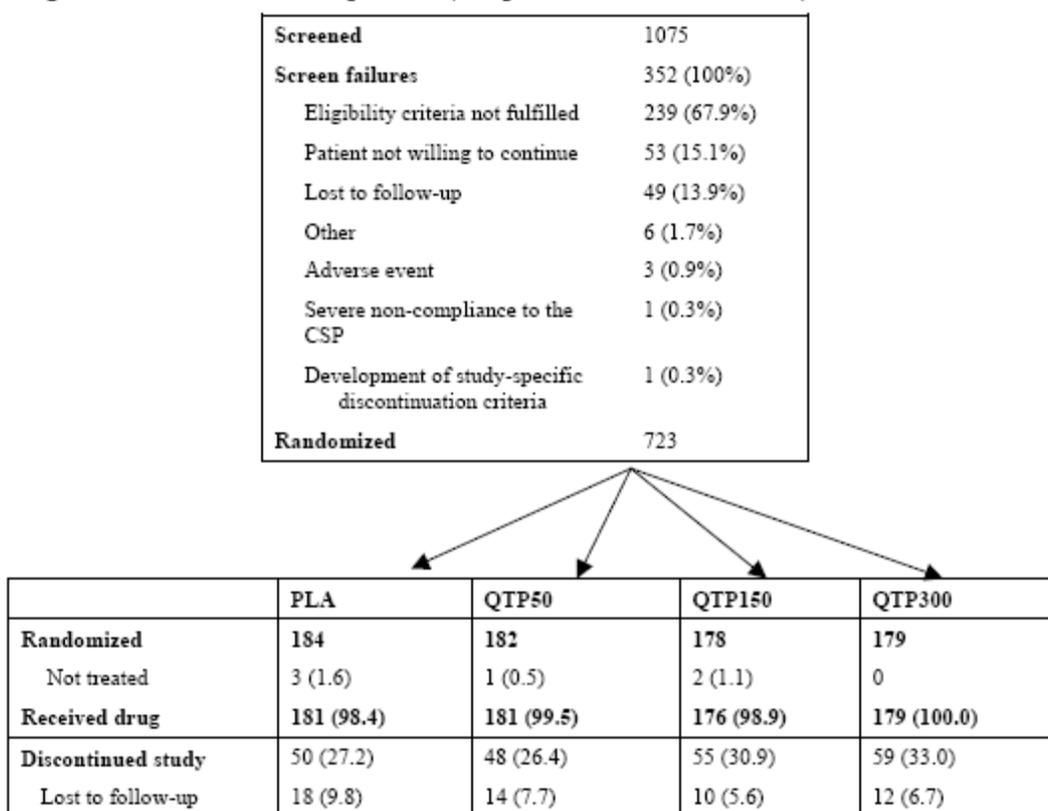
It was planned to randomly assign 712 patients to obtain a total of 664 evaluable patients (166 per treatment group). The sample size calculation in this study was done to ensure an 80% power in demonstrating superior efficacy of the 150-mg and/or 300-mg quetiapine XR doses over placebo with regard to the primary outcome variable, change in MADRS total score from randomization to Week 6. The appropriate sample size was attained by assuming an anticipated difference of 3.5 unit difference from placebo, with a between-patient variability (standard deviation) of 9 for the change in MADRS total score from baseline to Week 6. Because of multiplicity considerations, a 2-sided test at  $\alpha = 0.025$  and a power of 90% for each of the 2 high doses were assumed. This yields a planned sample size of 166 for each of the 4 arms, and 664 in total.

#### **Duration of treatment**

An initial washout period of 7 to 28 days (depending on the medications involved) was followed by a double-blind treatment period for up to 6 weeks (42 days). Eligible patients were randomly assigned to blinded treatment in a 1:1:1:1 ratio to the 50-mg/day

quetiapine XR treatment group, the 150-mg/day quetiapine XR treatment group, the 300-mg/day quetiapine XR treatment group, or the placebo treatment group. All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. Patients in the quetiapine XR 150 mg/day–group maintained this dose through the end of the randomized treatment period. Patients in the quetiapine XR 300-mg/day group were up-titrated to 300 mg/day on Day 5, and then maintained this dose through the end of the randomized treatment period. Following completion of the 6 week randomization period, patients participated in a 2-week post-treatment period. During the post-treatment period, patients were asked to call in to an Interactive Voice Response System (IVRS) to participate in an assessment of discontinuation symptoms assessed by the Treatment Discontinuation Signs and Symptoms (TDSS) scale and return to the study center for 2 post-treatment visits.

**Figure 3 Patient disposition (completion or discontinuation)**



	PLA	QTP50	QTP150	QTP300
Adverse event	11 (6.0)	15 (8.2)	25 (14.0)	34 (19.0)
Development of study-specific discontinuation criteria	1 (0.5)	3 (1.6)	0	1 (0.6)
Patient not willing to continue	10 (5.4)	9 (4.9)	9 (5.1)	8 (4.5)
Condition under investigation worsened	4 (2.2)	0	1 (0.6)	0
Severe non-compliance to study protocol	2 (1.1)	6 (3.3)	8 (4.5)	3 (1.7)
Eligibility criteria not fulfilled	1 (0.5)	0	2 (1.1)	0
Other	3 (1.6)	1 (0.5)	0	1 (0.6)
<b>Completed 6-week randomized treatment period</b>	<b>134 (72.8)</b>	<b>134 (73.6)</b>	<b>123 (69.1)</b>	<b>120 (67.0)</b>
<b>Completed study<sup>a</sup></b>	<b>95 (51.6)</b>	<b>103 (56.6)</b>	<b>89 (50.0)</b>	<b>86 (48.0)</b>

<sup>a</sup> Patients who completed the randomization phase plus the 2-week follow-up period.

In total, 1075 patients were screened for possible study participation. Of those, 723 qualified and were assigned to randomized treatment on Day 1. Of the 352 patients who did not qualify, 68% (239 patients) were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 184 to placebo, 182 to quetiapine XR 50 mg/day, 178 to quetiapine XR 150 mg/day, and 179 to quetiapine XR 300 mg/day.

Overall, the discontinuation rate was highest in the quetiapine XR 300-mg/day group (33%) followed by the quetiapine XR 150-mg/day group (31%), the quetiapine XR 50-mg/day group (26%) and the placebo group (27%). The most common reason for withdrawal was an adverse event. There was a dose-related increase in the rate of discontinuation due to AEs across the quetiapine XR groups. The rates of discontinuation due to AEs were higher in the quetiapine XR 50-mg/day group (19%), 150-mg/day group (14%), and 300-mg/day group (8%) when compared to placebo (6%). Loss to follow-up was the second most common reason for discontinuation and occurred with the highest frequency in the placebo group.

In patients with MDD, all doses of quetiapine XR (50 mg/day, 150 mg/day, and 300 mg/day) were superior to placebo in reducing the level of depressive symptoms as demonstrated by the statistically significant change from randomization to Week 6 in the MADRS total score. Overall, results from the secondary outcome variables supported the primary objective. MADRS total score was improved in all quetiapine groups relative to placebo by Day 4. The quetiapine XR groups demonstrated greater MADRS response, MADRS remission, reduction in the HAM-A total score, CGI-S and CGI-I scores, and improvement in HAM-A psychic anxiety subscale score in comparison to the placebo group. Improvements in MADRS, HAM-D, HAM-A, and PSQI scores indicated improved sleep quality with quetiapine XR treatment. However, in the evaluation of health-related quality of life with Q-LES-Q, the

efficacy of quetiapine XR over placebo was not demonstrated.

**Table 17 MADRS total score change from randomization to Week 6 (LOCF, MITT analysis set)**

		PLA N=178	QTP50 N=178	QTP150 N=168	QTP300 N=176
N <sup>a</sup>		178	178	168	176
Randomization <sup>b</sup>	Mean (SD)	30.5 (5.2)	30.9 (4.5)	30.9 (5.0)	30.6 (4.8)
Week 6	Mean (SD)	19.8 (10.6)	17.6 (10.4)	16.7 (10.2)	16.8 (9.8)
Change	Mean (SD)	-10.7 (10.1)	-13.3 (10.2)	-14.3 (9.9)	-13.8 (10.2)
ANCOVA results	LS mean	-11.07	-13.56	-14.50	-14.18
	95% CI	-12.79 to -9.34	-15.29 to -11.83	-16.26 to -12.74	-15.91 to -12.45

**Table 17 MADRS total score change from randomization to Week 6 (LOCF, MITT analysis set)**

		PLA N=178	QTP50 N=178	QTP150 N=168	QTP300 N=176
Difference vs PLA	Est. difference	NA	-2.50	-3.44	-3.11
	95% CI	NA	-4.48 to -0.51	-5.45 to -1.42	-5.10 to -1.12
	p-value	NA	0.014	<0.001	0.002
	Adjusted p-value <sup>c</sup>	NA	0.042	0.002	0.004

<sup>a</sup> Number of patients with a value at randomization and at least one post-randomization value. The mean value for change from randomization was calculated for these patients.  
<sup>b</sup> The mean value at randomization was calculated based on values at randomization for all patients in the MITT analysis set.  
<sup>c</sup> P-values were adjusted using the tree-gatekeeping procedure described in Section 5.7.4.1.  
 ANCOVA Analysis of covariance. CI Confidence interval. Est. Estimated. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Asberg Depression Rating Scale. MITT Modified intention-to-treat. N Number of patients in treatment group. NA Not applicable. PLA Placebo. QTP Quetiapine XR. SD Standard deviation.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

## STUDY 2

### **A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended Release (SEROQUEL XR) as Mono-Therapy in the Treatment of Adult Patients with Major Depressive Disorder (OPAL STUDY)**

#### **International co-ordinating investigator**

Andrew J. Cutler, MD  
 Florida Clinical Research Center  
 3914 SR 64 East  
 Bradenton, FL 34208

### **Study center(s)**

This study was conducted at 38 centers in the United States.

### **Study design**

This was an 8-week, multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled, Phase III study of the efficacy and safety of quetiapine XR 150 mg/day and 300 mg/day in the treatment of patients with MDD versus placebo and duloxetine 60 mg. This study consisted of an up to 28-day enrollment and washout period, a 6-week randomized treatment period, and a 2-week post-treatment period that included titrated dose decreases during the first post-treatment week for patients randomly assigned to the quetiapine XR 300-mg/day and duloxetine 60-mg dose groups.

### **Target population and sample size**

Male and female patients, 18 to 65 years old inclusive, with documented clinical diagnosis using the Mini-International Neuropsychiatric Interview (MINI) and meeting the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV) of either 296.2x Major Depressive Disorder, Single Episode, or 296.3x Major Depressive Disorder, Recurrent.

The patients had to have a Hamilton Rating Scale for Depression (HAM-D) score  $\geq 22$  to be eligible for the study. The aim of this study was to randomize a patient population with approximately 40% of the patients having a HAM-D score of  $\geq 28$ .

The sample size calculation in this study was done to ensure an 80% power in demonstrating superior efficacy of each of the 2 quetiapine XR doses over placebo with regard to the primary outcome variable, change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization to Week 6. The appropriate sample size was attained by assuming an anticipated difference of 3.5 units from placebo and a standard deviation of 9 for the change in MADRS total score from randomization to Week 6. Based on a 2-sided test at a 5% significance level (ie,  $\alpha=0.05$ ), it was planned to randomize a sample size of 140 per treatment group and 560 in total to ensure a power of 90% in each individual comparison and an overall power of at least 80%. Assuming based on earlier studies that 93% of all patients assigned to randomized treatment were expected to be evaluable patients (to be included in the modified intent-to-treat [MITT] group), a total of about 600 patients assigned to randomized treatment were required to obtain 140 evaluable patients per treatment group. A total of 612 patients were assigned to randomized treatment, of whom 610 received treatment and were in the safety analysis set and 587 were included in the MITT analysis set. The study was not powered for a comparison of quetiapine XR versus duloxetine.

### **Duration of treatment**

An initial washout period of 7 to 28 days (depending on the medications involved) was followed by a double-blind treatment period for up to 6 weeks (42 days). During a 2-week post-treatment period, patients randomly assigned to the quetiapine XR 300-mg/day dose

group and the duloxetine 60-mg dose groups took titrated decreased doses of their randomly assigned study medication from Day 43 (final treatment visit) to Post-treatment Day 6. During the 2-week down-titration period, patients assigned to randomized treatment with quetiapine XR 150 mg/day received placebo from Day 43 (Final visit) to Day 49 (Posttreatment Day 6). For all groups, study drugs were stopped after Day 49. All patients randomly assigned to treatment who completed the treatment period and assessments were asked to call in to an Interactive Voice Response System (IVRS) to participate in an assessment of discontinuation symptoms assessed by the Treatment Discontinuation Signs and Symptoms (TDSS) scale and return to the study center for 2 Post-treatment visits.

**Figure 3 Patient disposition (completion or discontinuation)**

Screened	912			
Screen failures	299			
Lost to follow-up	36			
Adverse event	3			
Eligibility criteria not fulfilled	213			
Patient not willing to continue	44			
Severe noncompliance to protocol	1			
Other	2			
<b>Randomized</b>	<b>612<sup>a</sup></b>			

	PLA	QTP150	QTP300	DUL
<b>Randomized</b>	<b>157 (100.0)</b>	<b>152 (100.0)</b>	<b>152 (100.0)</b>	<b>151 (100.0)</b>
Not treated <sup>b</sup>	0	0	0	2
<b>Received drug</b>	<b>157</b>	<b>152</b>	<b>152</b>	<b>149</b>
<b>Discontinued study</b>	<b>33 (21.0)</b>	<b>52 (34.2)</b>	<b>39 (25.7)</b>	<b>46 (30.5)</b>
Adverse event	7 (4.5)	30 (19.7)	23 (15.1)	20 (13.1)
Condition under investigation worsened	3 (1.9)	0	0	2 (1.3)
Death	0	1 (0.7)	0	0
Development of study-specific discontinuation criteria	1 (0.6)	1 (0.7)	1 (0.7)	1 (0.7)
Eligibility criteria not fulfilled	0	1 (0.7)	0	2 (1.3)
Other	1 (0.6)	0	1 (0.7)	2 (1.3)
Severe noncompliance to the protocol	3 (1.9)	2 (1.3)	1 (0.7)	0
Lost to follow-up	9 (5.7)	10 (6.6)	6 (3.9)	7 (4.6)
Not willing to continue	9 (5.7)	7 (4.6)	7 (4.6)	12 (7.9)
<b>Completed 6-week randomized treatment period</b>	<b>124 (79.0)</b>	<b>100 (65.8)</b>	<b>113 (74.3)</b>	<b>105 (69.5)</b>
<b>Completed study<sup>c</sup></b>	<b>100 (63.7)</b>	<b>73 (48.0)</b>	<b>92 (60.5)</b>	<b>71 (47.0)</b>

<sup>a</sup> Patient E1009500 was screened for this study but mistakenly assigned to randomized treatment in another study. This patient was counted as screened for this study and was not counted as randomized in this study, but was not counted as a screen failure.

<sup>b</sup> Patients not treated are also included in the discontinued from study treatment analysis set due to development of study-specific discontinuation criteria.

<sup>c</sup> Completed the randomization period and the 2-week follow-up period (TDSS).

DUL Duloxetine. PLA Placebo. QTP Quetiapine XR.

In total, 912 patients were screened for possible study participation. Of those, 612 qualified and were assigned to randomized treatment on Day 1. Of the 299 patients who did not qualify, 71.2% (213 patients) were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 157 to placebo, 152 to quetiapine XR 150 mg/day, 152 to quetiapine XR 300 mg/day and 151 to duloxetine 60 mg/day. Of the 612 patients assigned to randomized treatment, 2 did not receive any study medication (both in the duloxetine group).

Overall, 21% of the placebo group, 34.2% quetiapine XR 150-mg/day group, 25.7% of the quetiapine XR 300-mg/day group, and 30.5% of the duloxetine group discontinued the study during randomized treatment. Discontinuations due worsening of the condition under investigation occurred in 1.9% of placebo patients and 1.3% of duloxetine patients. None of the quetiapine XR patients at either dose discontinued for this reason. The rate of discontinuation due to AE was higher in the quetiapine XR 150-mg/day group (19.7%), quetiapine XR 300-mg/day group (15.1%), and the duloxetine group (13.2%) than in the placebo group (4.5%). “Adverse event” was the most common reason for discontinuation in all but the placebo groups. Discontinuations due to loss to follow-up and patient not willing to continue occurred at a similar rate in all of the treatment groups.

Approximately 72% of patients completed the randomized treatment portion of the study. Of those patients who completed randomized treatment, 80.6% of placebo patients, 73.0% of quetiapine XR 150-mg/day patients, 81.4% of quetiapine XR 300-mg/day patients, and 67.6% of duloxetine patients completed the 2-week follow-up (TDSS) period.

**Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)**

Outcome variable	PLA N=152	QTP150 N=147	QTP300 N=147	DUL N=141
MADRS LS mean change from randomization	-11.18	-14.81 <sup>a</sup>	-15.29 <sup>a</sup>	-14.64 <sup>a</sup>
Proportion with MADRS response (decrease in MADRS total score $\geq$ 50%)	36.2%	54.4% <sup>b</sup>	55.1% <sup>a</sup>	49.6% <sup>c</sup>
Proportion with MADRS remission (total score $\leq$ 8)	20.4%	26.5%	32.0% <sup>c</sup>	31.9% <sup>c</sup>
HAM-D LS mean change from randomization	-10.26	-13.12 <sup>a</sup>	-14.02 <sup>a</sup>	-12.37 <sup>c</sup>
HAM-D Item 1 LS mean change from randomization	-1.07	-1.49 <sup>a</sup>	-1.56 <sup>a</sup>	-1.53 <sup>a</sup>
CGI-S LS mean change from randomization	-1.06	-1.43 <sup>b</sup>	-1.60 <sup>a</sup>	-1.53 <sup>a</sup>
Proportion improved on CGI-I	39.5%	54.1% <sup>c</sup>	59.2% <sup>a</sup>	56.7% <sup>b</sup>
Q-LES-Q % maximum total score LS mean change from randomization	11.26	13.68	13.59	16.69 <sup>b</sup>
HAM-A total score LS mean change from randomization	-5.55	-7.76 <sup>b</sup>	-7.38 <sup>b</sup>	-7.83 <sup>a</sup>

<sup>a</sup> p $\leq$ 0.001 comparison with placebo.

<sup>b</sup> p $\leq$ 0.01 comparison with placebo.

<sup>c</sup> p $\leq$ 0.05 comparison with placebo.

CGI-S Clinical Global Impression Severity scale. CGI-I Clinical Global Impression Improvement scale. DUL Duloxetine. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. MITT Modified intention-to-treat. PLA Placebo. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR.

Note: For the analyses of MADRS and Q-LES-Q percent maximum total score change from randomization for the quetiapine XR groups, p-values were adjusted and compared with  $\alpha=0.05$  using the Simes-Hommel procedure within the step-wise sequential testing strategy. P-values for the comparison between duloxetine and placebo and between duloxetine and quetiapine XR were not adjusted.

In patients with MDD, quetiapine XR at a dose of 150 mg/day or 300 mg/day was superior to

placebo in reducing the level of depressive symptoms as demonstrated by the statistically significant change from randomization to Week 6 in the MADRS total score. Both quetiapine XR groups showed a greater improvement by Week 1 of treatment ( $p=0.002$  and  $p=0.004$  for 150 mg/day and 300 mg/day, respectively).

The quetiapine XR 150- and 300-mg groups received mean daily doses of 124.7 and 244.8, respectively, and were on treatment for a mean of 37.7 and 40.4 days, respectively, during the 6-week randomized period.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

### **STUDY 3**

#### **A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended Release (SEROQUEL XR) as Mono-Therapy in the Treatment of Adult Patients with Major Depressive Disorder (OPAL STUDY)**

##### **International co-ordinating investigator**

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##### **Study center(s)**

This study was conducted at 35 sites in the United States.

##### **Study design**

This was a 10-week, multicenter, double-dummy, randomized, parallel-group, placebo controlled Phase III study of the efficacy and safety of quetiapine XR given as monotherapy in the treatment of patients with MDD. The study consisted of an up to 28-day enrollment period, an 8-week randomized treatment period, and a 2-week post-treatment period. All quetiapine XR patients initiated treatment on quetiapine XR 50 mg/day and were up-titrated to 150 mg/day at Day 3. Placebo patients received matched placebo according to the same treatment plan. After 2 weeks of treatment, patients with an inadequate response (defined as failure to achieve a  $\geq 20\%$  improvement from randomization in MADRS total score) were up-titrated to twice their original dose (300 mg/day quetiapine XR or matching placebo). Investigators were blinded to the criterion defining inadequate response (ie, the criterion for inadequate response was defined in a document separate from the study protocol and not

shared with the investigator) and were blinded to dose increase. At the end of 8 weeks of randomized treatment, all investigational product was discontinued and patients underwent a 2-week post-treatment follow-up period.

### **Duration of treatment**

An initial washout period of up to 28 days (depending on the medications involved) was followed by an 8-week, double-blind randomized treatment period. After 2 weeks of treatment, patients with an inadequate response were treated with double the randomized dose (ie, quetiapine XR 300 mg/day or placebo). The 8-week, double-blind treatment period was followed by a 2-week follow-up period.

**Figure 2 Patient disposition (completion or discontinuation)**

Screened	513
Screen failures	203
Eligibility criteria not fulfilled	154
Other	3
Lost to follow-up	16
Patient not willing to continue	30
<b>Randomized</b>	<b>310</b>

	PLA	QTP
<b>Randomized</b>	<b>156</b>	<b>154</b>
Not treated <sup>a</sup>	1	2
<b>Received drug</b>	<b>155 (99.4%)</b>	<b>152 (98.7%)</b>
<b>Adequate response<sup>b</sup></b>	102 (74.5%)	107 (82.9%)
<b>Inadequate response<sup>b</sup></b>	35 (25.5%)	22 (17.1%)
<b>Discontinued study</b>	<b>45 (28.8%)</b>	<b>46 (29.9%)</b>
Adverse event	4 (2.6%)	13 (8.4%)
Eligibility criteria not fulfilled	1 (0.6%)	2 (1.3%)
Lack of therapeutic response	7 (4.5%)	7 (4.5%)
Other	3 (1.9%)	0
Severe noncompliance to the protocol	3 (1.9%)	1 (0.6%)
Did not complete $\geq 50$ days of treatment	1 (0.6%)	0
Lost to follow-up	12 (7.7%)	11 (7.1%)
Not willing to continue with study	14 (9.0%)	12 (7.8%)
<b>Completed 8-week randomized treatment period</b>	<b>111 (71.2%)</b>	<b>108 (70.1%)</b>
<b>Completed study<sup>c</sup></b>	<b>78 (50.0%)</b>	<b>81 (52.6%)</b>

<sup>a</sup> Patients not treated are also included in the discontinued from study treatment analysis set due to development of study-specific discontinuation criteria.

<sup>b</sup> Patients with inadequate response after 2 weeks of treatment (defined as a failure to achieve  $\geq 20\%$  improvement from randomization in MADRS total score) were up-titrated to double their initial dose (300 mg quetiapine XR or double the placebo dose). Those with an adequate response remained at their initial dose (150 mg quetiapine XR or a matching placebo dose). Percentages are based on the numbers of

In total, 513 patients were screened for possible study participation. Of those, 310 qualified and were assigned to randomized treatment on Day 1. Of the 203 patients who did not qualify, 154 patients were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 156 to placebo and 154 to quetiapine XR. Of the 310 randomized patients, 3 patients

(1 and 2 patients in the placebo and quetiapine XR groups, respectively) did not receive any study medication.

Based on the number of patients still receiving randomized treatment at Week 2, a total of 35 of 137 (26%) and 22 of 129 (17%) patients in the placebo and quetiapine XR groups, respectively, met the criterion for inadequate response (ie, were up-titrated to double the initial randomized dose after 2 weeks of treatment for failing to show  $\geq 20\%$  improvement in MADRS total score from randomization).

Overall, 28.8% of the placebo group and 29.9% of the quetiapine XR group discontinued the study during randomized treatment. “Subject not willing to continue with study” was the main reason for withdrawal in placebo-treated patients, and AE was the main reason for discontinuation among quetiapine XR patients. A similar percentage of patients in both treatment groups discontinued the study because they were not willing to continue the study (7.8% and 9.0% in the quetiapine XR and placebo groups, respectively) or were lost to followup (7.1% and 7.7%, respectively). Of patients who completed the randomized treatment period, 70.3% of placebo patients and 75.0% of quetiapine XR patients completed the TDSS follow-up period.

Approximately 71% of patients completed the randomized treatment period of the study, with similar rates of completion in the quetiapine XR group compared to placebo. Of patients who completed the randomized treatment period, 70.3% and 75.0% of placebo and quetiapine XR patients, respectively, completed the 2-week follow-up period (TDSS).

**Table S3 Efficacy results at Week 8 (LOCF, MITT analysis set)**

Outcome variable	PLA N=152	QTP N=147
MADRS total score LS mean change from randomization	-13.1	-16.49 <sup>a</sup>
Proportion with MADRS response (decrease in MADRS total score of $\geq 50\%$ )	48.0%	61.9% <sup>b</sup>
Proportion with MADRS remission (total score $\leq 8$ )	25.0%	34.7% <sup>c</sup>
HAM-D total score LS mean change from randomization	-12.35	-14.75 <sup>b</sup>
HAM-D Item 1 LS mean change from randomization	-1.40	-1.71 <sup>b</sup>
CGI-S total score LS mean change from randomization	-1.24	-1.64 <sup>a</sup>
Proportion improved on CGI-I	52.0%	63.3% <sup>b</sup>
Q-LES-Q % maximum total score LS mean change from randomization	11.93	13.80
HAM-A total score LS mean change from randomization	-7.70	-9.14 <sup>b</sup>

<sup>a</sup> p<0.01 comparison with placebo.  
<sup>b</sup> p<0.05 comparison with placebo.  
<sup>c</sup> p=0.052 comparison with placebo.

In patients with MDD, quetiapine XR was superior to placebo in reducing depressive

symptoms as demonstrated by the statistically significant mean change from randomization to Week 8 in the MADRS total score.

Overall, results from the secondary outcome variables supported the primary objective.

The quetiapine XR group received a mean daily dose of 162.2 mg, reflective of the large percentage of patients (83%) who remained at the 150-mg dose throughout the study.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

#### **STUDY 4**

### **A Multi-Centre, Double-Blind, Randomised, Parallel Group, Placebo-Controlled and Active Controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended Release (SEROQUEL XR™) as Mono-Therapy in the Treatment of Adult Patients with Major Depressive Disorder (AMBER STUDY)**

#### **International co-ordinating investigator**

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#### **Study center(s)**

There were 471 patients assigned to randomized treatment at 54 centers in Finland, Spain, Korea, Malaysia, China, Philippines, Canada, Mexico, and South Africa.

#### **Study design**

This was a 10-week, multicenter, double-dummy, randomized, parallel-group, placebocontrolled Phase III study of the efficacy and safety of quetiapine XR in the treatment of patients with MDD versus placebo. Escitalopram was added as an active control. This study consisted of an up to 28-day enrollment and washout period, an 8-week randomized treatment period, and a 2-week follow-up (treatment discontinuation signs and symptoms [TDSS]) period. All quetiapine XR patients initiated treatment on quetiapine XR 50 mg/day and were up-titrated to 150 mg/day at Day 3. All escitalopram patients initiated treatment on escitalopram 10 mg/day. After 2 weeks of treatment, patients in each treatment group with an inadequate response (defined as failure to achieve a  $\geq 20\%$  reduction in MADRS total score)

were up-titrated to twice their original dose (300 mg/day quetiapine XR, 20 mg/day escitalopram, or placebo). Investigators were blinded to the criterion defining inadequate response (ie, the criterion for inadequate response was defined in a document separate from the study protocol and not shared with the investigator) and were blinded to actual dose. At the end of the 8 weeks of randomized treatment, patients underwent a 2-week follow-up (TDSS) period including 1 week of down-titration in a blinded fashion. Patients on quetiapine XR 150 mg/day and escitalopram 10 mg/day received placebo for 1 week, whereas patients on quetiapine XR 300 mg/day and escitalopram 20 mg/day underwent a 1-week down-titration of quetiapine XR and escitalopram, to half of the 8-week dose (ie, to 150 mg/day and 10 mg/day, respectively). At the end of Week 9, all investigational product treatment was discontinued.

### **Duration of treatment**

An initial washout period of 7 to 28 days (depending on the medications involved) was followed by an 8-week, double-blind treatment period. After 2 weeks of treatment, patients with an inadequate response were treated with double the randomized dose (ie, quetiapine XR 300 mg/day or escitalopram 20 mg/day). The 8-week, double-blind treatment period was followed by a 2-week follow-up (TDSS) period that included 1 week of down-titration in a blinded fashion.

**Figure 2 Patient disposition (completion or discontinuation)**

<b>Screened</b>	660		
<b>Screen failures</b>	189		
Eligibility criteria not fulfilled	107 (16.2%)		
Patient not willing to continue	48 (7.3%)		
Lost to follow-up	27 (4.1%)		
Adverse event	1 (0.2%)		
Death	1 (0.2%)		
Severe noncompliance	1 (0.2%)		
Other	4 (0.6%)		
<b>Randomized</b>	471		

	PLA	QTP	ESC
<b>Randomized</b>	<b>157</b>	<b>157</b>	<b>157</b>
Not treated <sup>a</sup>	2 (1.3%)	0	1 (0.6%)
<b>Received drug</b>	<b>155 (98.7%)</b>	<b>157 (100.0%)</b>	<b>156 (99.4%)</b>
Patients with inadequate response <sup>b,c</sup>	40 (26.1%)	20 (13.0%)	36 (23.7%)
Patients with adequate response <sup>c</sup>	113 (73.9%)	134 (87.0%)	116 (76.3%)
<b>Discontinued study</b>	<b>40 (25.5%)</b>	<b>50 (31.8%)</b>	<b>39 (24.8%)</b>
Adverse event	7 (4.5%)	24 (15.3%)	9 (5.7%)
Condition under investigation not improved	7 (4.5%)	4 (2.5%)	6 (3.8%)
Eligibility criteria not fulfilled	2 (1.3%)	0	1 (0.6%)
Severe non-compliance with the protocol	2 (1.3%)	2 (1.3%)	2 (1.3%)
Patient lost to follow-up	9 (5.7%)	4 (2.5%)	5 (3.2%)
Patient not willing to continue	12 (7.6%)	14 (8.9)	12 (7.6%)
Other	1 (0.6%)	2 (1.3%)	4 (2.5%)
<b>Completed 8-week randomized treatment period</b>	<b>117 (74.5%)</b>	<b>107 (68.2%)</b>	<b>118 (75.2%)</b>
<b>Completed study<sup>d</sup></b>	<b>73 (46.5%)</b>	<b>81 (51.6%)</b>	<b>69 (43.9%)</b>

<sup>a</sup> Patients not treated are also included in the discontinued from study treatment analysis set due to development of study-specific discontinuation criteria.

<sup>b</sup> Patients who failed to meet the criterion of adequate response ( $\geq 20\%$  reduction in MADRS total score after 2 weeks of treatment) were up-titrated to double the initial randomized dose for the remaining 6 weeks of randomized treatment.

<sup>c</sup> Percentages based on MITT analysis set

<sup>d</sup> Completed the randomization period and the 2-week follow-up (TDSS) period.

ESC Escitalopram. PLA Placebo. QTP Quetiapine XR.

In total, 660 patients were screened for possible study participation. Of those, 471 qualified and were assigned to randomized treatment on Day 1. Of the 189 patients who did not qualify, 107 patients were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 157 to placebo, 157 to quetiapine XR 150 mg/day, and 157 to escitalopram 10 mg/day. Of the 471 patients assigned to randomized treatment, 3 patients (2 patients in the placebo group and 1 patient in the escitalopram group) did not receive any study medication. The number of patients assigned to randomized treatment categorized by country include:

Canada, 100; China, 40; Finland, 39; Korea, 31; Malaysia, 24; South Africa, 108; Spain, 17; Philippines, 38; and Mexico, 74 (see [Table 11.1.1.2](#), Section 11.1). For each country, the proportions of patients assigned to each treatment group were generally well-balanced with the exception of Mexico (15%, 20%, and 12% of patients were randomized to the placebo, quetiapine XR, and escitalopram groups, respectively).

A total of 26.1%, 13.0%, and 23.7% of patients in the placebo, quetiapine XR, and escitalopram groups, respectively, met the criterion for inadequate response (ie, failed to achieve a  $\geq 20\%$  reduction in MADRS total score after 2 weeks of randomized treatment). Those patients having an inadequate response were up-titrated to double the initial dose. Overall, 25.5% of the placebo group, 31.8% of the quetiapine XR group, and 24.8% of the escitalopram group discontinued the study during randomized treatment. Discontinuations due to lack of improvement in condition under investigation occurred less frequently in the quetiapine XR group (2.5%) than either the placebo or escitalopram groups (4.5% and 3.8%, respectively). The rate of discontinuation due to AEs was higher in the quetiapine XR group (15.3%) compared to the placebo and escitalopram groups (4.5% and 5.7%, respectively). A total of 5.7%, 2.5%, and 3.2% of patients in the placebo, quetiapine XR, and escitalopram groups were lost to follow-up.

Approximately 73% of patients completed the randomized treatment period of the study, with the lowest rate of completion occurring in the quetiapine XR group (68.2% vs. 74.5% in the placebo group and 75.2% in the escitalopram group). Of patients who completed the randomized treatment phase of the study, 62.4%, 75.7%, and 58.5% of placebo, quetiapine XR, and escitalopram patients, respectively, completed the 2-week follow-up (TDSS) period.

**Table S3 Efficacy results at Week 8 (LOCF, MITT analysis set)**

Outcome variable	PLA N=153	QTP N=154	ESC N=152
MADRS total score, LS mean change from randomization	-15.61	-17.21	-16.73
Proportion with MADRS response (total score $\geq$ 50% reduction from baseline)	51.0%	60.4%	59.9%
Proportion with MADRS remission (total score $\leq$ 8)	35.3%	35.7%	40.8%
HAM-D total score, LS mean change from randomization	-13.75	-14.99	-14.70
HAM-D Item 1 score, LS mean change from randomization	-1.41	-1.57	-1.65
HAM-A total score, LS mean change from randomization	-8.28	-9.44	-9.67
CGI-S score, LS mean change from randomization	-1.76	-1.83	-1.85
Proportion improved on CGI-I	58.8%	61.4%	64.2%
Q-LES-Q % maximum total score, LS mean change from randomization	13.55	13.46	16.00

CGI-I Clinical Global Impression - Improvement scale. CGI-S Clinical Global Impression - Severity scale. ESC Escitalopram. MADRS Montgomery-Åsberg Depression Rating Scale. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. LS Least square. MITT Modified intention-to-treat. PLA Placebo. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR.

The quetiapine XR group showed a greater mean change in MADRS total score at Week 8 compared with placebo; however, superiority over placebo was not demonstrated based on the nominal p-value when using the primary analysis method (least square [LS] mean change from randomization for quetiapine XR versus placebo of -1.6,  $p=0.174$ ). Similar results were observed for the escitalopram group in mean change in MADRS total score at Week 8 when compared with placebo (LS mean change from randomization for escitalopram versus placebo of -1.1,  $p=0.346$ ). Similar results were also observed for quetiapine XR versus placebo when using the PP analysis set (LOCF) (LS mean change from randomization for quetiapine XR versus placebo of -1.7,  $p=0.175$ ).

The quetiapine group received a mean daily dose of 139.8 mg, reflective of the large percentage of patients (87.0%) who remained at the 150-mg dose throughout the study.

This study was not significant.

## STUDY 6

### **A Multicenter, Double-blind, Randomized, Parallel-group, Placebocontrolled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended-release (SEROQUEL XR™) in Combination with an Antidepressant in the Treatment of Patients with Major Depressive Disorder with Inadequate Response to an Antidepressant Treatment (Pearl Study)**

Co-ordinating investigator

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### **Study center(s)**

This study was conducted in the USA (56 centers).

### **Study design**

This was an 8-week, multicenter, double-blind, randomized, parallel-group, placebocontrolled, double-dummy, Phase III study of the efficacy and safety of quetiapine XR 150 mg/day and 300 mg/day in combination with an antidepressant in the treatment of patients with MDD who have shown an inadequate response to antidepressant monotherapy. The study comprised 3 periods: an enrollment and washout period of up to 14 days (for the discontinuation of all prohibited medications), a 6-week randomized treatment period, and a 2-week follow-up period. Patients continued to maintain the same antidepressant therapy from the period beginning at enrollment through the end of double-blind treatment.

### **Duration of treatment**

Eligible patients underwent a washout period of up to 14 days for the discontinuation of all prohibited medications. Patients then entered a 6-week treatment period, when they were randomly assigned to blinded treatment in a 1:1:1 ratio to 150 mg/day quetiapine XR, 300 mg/day quetiapine XR, or placebo (each in combination with the ongoing antidepressant treatment). All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. Patients in the quetiapine XR 150-mg/day group maintained this dose through the end of the randomized treatment period. Patients in the quetiapine XR 300-mg/day group were up-titrated to 300 mg/day on Day 5, and then maintained this dose through the end of the randomized treatment period. The ongoing treatment with the antidepressant was maintained at the same dose throughout the study. During the 2-week follow-up period, no down-titration of quetiapine XR was performed since the dose of antidepressant was maintained.

In total, 659 patients were screened for possible study participation. Of those, 446 qualified and were assigned to randomized treatment on Day 1. Of the 213 patients who did not qualify, 158 patients (74%) were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 148 to placebo, 148 to quetiapine XR 150 mg/day, and 150 to quetiapine XR 300 mg/day. Of the 446 patients assigned to randomized treatment, 1 patient (assigned to the quetiapine XR 300-mg/day group) did not receive any study medication.

Overall, the discontinuation rate during the 6-week randomized treatment period was highest in the quetiapine XR 300-mg/day group (30.0%) followed by the quetiapine XR 150-mg/day group (23.0%), and the placebo group (15.5%). Discontinuations due to lack of therapeutic response were more frequent in the placebo group (2.7%) than in the quetiapine XR groups (1.4% in the 150-mg/day group, and 0% in the 300-mg/day group). The percentages of patients lost to follow-up or not willing to continue were low (<7%); these 2 reasons for discontinuation were more prevalent among placebo patients compared with those treated with either dose of quetiapine XR. There was an apparent dose-related increase in the rate of discontinuation due to AEs across the quetiapine XR groups. The rate of discontinuation due to AEs was 18.0% and 10.8% in the quetiapine XR 300-mg/day and 150-mg/day groups, respectively, compared with 0.7% in the placebo group.

Approximately 77% of patients completed the randomized treatment period of the study, with higher rates of completion in the placebo group (85%) compared with the quetiapine XR groups (77% in the 150-mg/day group and 70% in the 300-mg/day group). Of those patients who completed the randomized treatment period, approximately 79% of patients in the placebo group, 81% of patients in the quetiapine XR 150-mg/day group, and 65% of those in the quetiapine XR 300-mg/day group completed the 2 week follow-up (TDSS) period. The overall completion rate for the study—through the end of the 2-week follow-up (TDSS) period—was approximately 67%, 62%, and 45% for patients in the placebo, quetiapine XR 150-mg/day, and quetiapine XR 300-mg/day groups, respectively.

**Figure 3 Patient disposition (completion or discontinuation)**

Screened	659
Screen failures	213
Lost to follow-up	6
Adverse event	3
Eligibility criteria not fulfilled	158
Development of study-specific discontinuation criteria	1
Patient not willing to continue	43
Other	2
<b>Randomized</b>	<b>446</b>

	PLA	QTP150	QTP300
<b>Randomized</b>	<b>148</b>	<b>148</b>	<b>150</b>
Not treated	0	0	1
<b>Received drug</b>	<b>148 (100%)</b>	<b>148 (100%)</b>	<b>149 (99.3%)</b>
<b>Discontinued study<sup>a</sup></b>	<b>23 (15.5%)</b>	<b>34 (23.0%)</b>	<b>45 (30.0%)</b>
Adverse event	1 (0.7%) <sup>b</sup>	16 (10.8%) <sup>c</sup>	27 (18.0%)
Eligibility criteria not fulfilled	0	1 (0.7%)	1 (0.7%)
Lack of therapeutic response	4 (2.7%)	2 (1.4%)	0
Severe non-compliance with the study protocol	0	2 (1.4%)	0
Did not complete ≥36 days of study treatment	0	1 (0.7%)	1 (0.7%)
Lost to follow-up	10 (6.8%)	8 (5.4%)	7 (4.7%)
Patient not willing to continue	8 (5.4%)	4 (2.7%)	6 (4.0%)
Other	0	0	3 (2.0%)
<b>Completed 6-week randomized treatment period</b>	<b>125 (84.5%)</b>	<b>114 (77.0%)</b>	<b>105 (70.0%)</b>
<b>Discontinued during post-Week 6 TDSS period<sup>a</sup></b>	<b>26 (17.6%)</b>	<b>22 (14.9%)</b>	<b>37 (24.7%)</b>
Adverse event	0	0	3 (2.0%)
Severe non-compliance with the study protocol	1 (0.7%)	1 (0.7%)	1 (0.7%)
Patient did not complete Day 14 TDSS assessment	6 (4.1%)	7 (4.7%)	9 (6.0%)
Lost to follow-up	3 (2.0%)	2 (1.4%)	4 (2.7%)
Patient not willing to continue	5 (3.4%)	3 (2.0%)	2 (1.3%)
Other	11 (7.4%)	9 (6.1%)	18 (12.0%)
<b>Completed study<sup>d</sup></b>	<b>99 (66.9%)</b>	<b>92 (62.2%)</b>	<b>68 (45.3%)</b>

<sup>a</sup> For reasons for withdrawal for individual patients, see Listing 12.2.1.2, Appendix 12.2.

<sup>b</sup> The 1 placebo patient (E1605429) had an onset of AE (ECG abnormalities) prior to randomization, but was discontinued due to this AE during the randomized treatment period.

**Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)**

Outcome variable	PLA N=143	QTP150 N=143	QTP300 N=146
MADRS total score, LS mean change from baseline	-11.70	-13.60	-14.70 <sup>b</sup>
Proportion with $\geq 50\%$ MADRS response	46.2%	51.7%	58.9% <sup>a</sup>
Proportion with MADRS remission (total score $\leq 8$ )	24.5%	35.0%	42.5% <sup>b</sup>
HAM-D total score, LS mean change from baseline	-10.80	-12.63 <sup>a</sup>	-13.53 <sup>b</sup>
HAM-D Item 1 score, LS mean change from baseline	-1.35	-1.53	-1.60
HAM-A total score, LS mean change from baseline	-6.67	-7.43	-8.50 <sup>a</sup>
CGI-S score, LS mean change from baseline	-1.23	-1.47	-1.52 <sup>a</sup>
Proportion improved on CGI-I	46.9%	58.0%	58.2% <sup>a</sup>
Q-LES-Q percent maximum total score, LS mean change from baseline	11.32	10.37	11.82

<sup>a</sup> p<0.05 comparison with placebo.

<sup>b</sup> p<0.01 comparison with placebo.

CGI-I Clinical Global Impression Improvement scale. CGI-S Clinical Global Impression Severity scale. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. MITT Modified intention-to-treat. PLA Placebo. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR.

Note: For the analyses of MADRS total score and Q-LES-Q % maximum total score change from baseline, p-values were adjusted and compared with  $\alpha=0.05$  using the Simes-Hommel procedure within the step-wise sequential testing strategy.

The mean change from baseline for both quetiapine XR treatment groups was superior to placebo at Week 1 (-5.95 in the placebo group; -9.06 for quetiapine XR 150 mg/day [p<0.001 vs placebo]; and -8.20 in the quetiapine XR 300 mg/day group [p=0.002 vs placebo]). Patients in the 300-mg/day group continued to demonstrate a statistically significant greater change in the MADRS total score compared with placebo throughout the 6 weeks of randomized treatment.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

## STUDY 7

### **A Multicenter, Double-blind, Randomized, Parallel-group, Placebocontrolled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended-release (SEROQUEL XR™) in Combination with an Antidepressant in the Treatment of Patients with Major Depressive Disorder with Inadequate Response to an Antidepressant Treatment (Onyx Study)**

**International co-ordinating investigator**

Prof HW Pretorius  
Weskoppies Hospital  
Out Patients Department  
Ketjen Street  
Pretoria West, South Africa 0001

### **Study center(s)**

Five hundred seventy-two patients were enrolled to obtain 493 patients assigned to randomized treatment in Europe, South Africa, North America, and Australia to yield 420 evaluable patients at 87 study sites.

### **Study design**

This was a 6-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled, double-dummy, phase III study of the efficacy and safety of quetiapine XR 150 mg/day and 300 mg/day in combination with an antidepressant in the treatment of patients with MDD who have shown an inadequate response to an antidepressant treatment. The randomized treatment period was preceded by a washout period of up to 14 days. Patients continued to maintain the same antidepressant therapy from the period beginning at enrollment through the end of double-blind treatment.

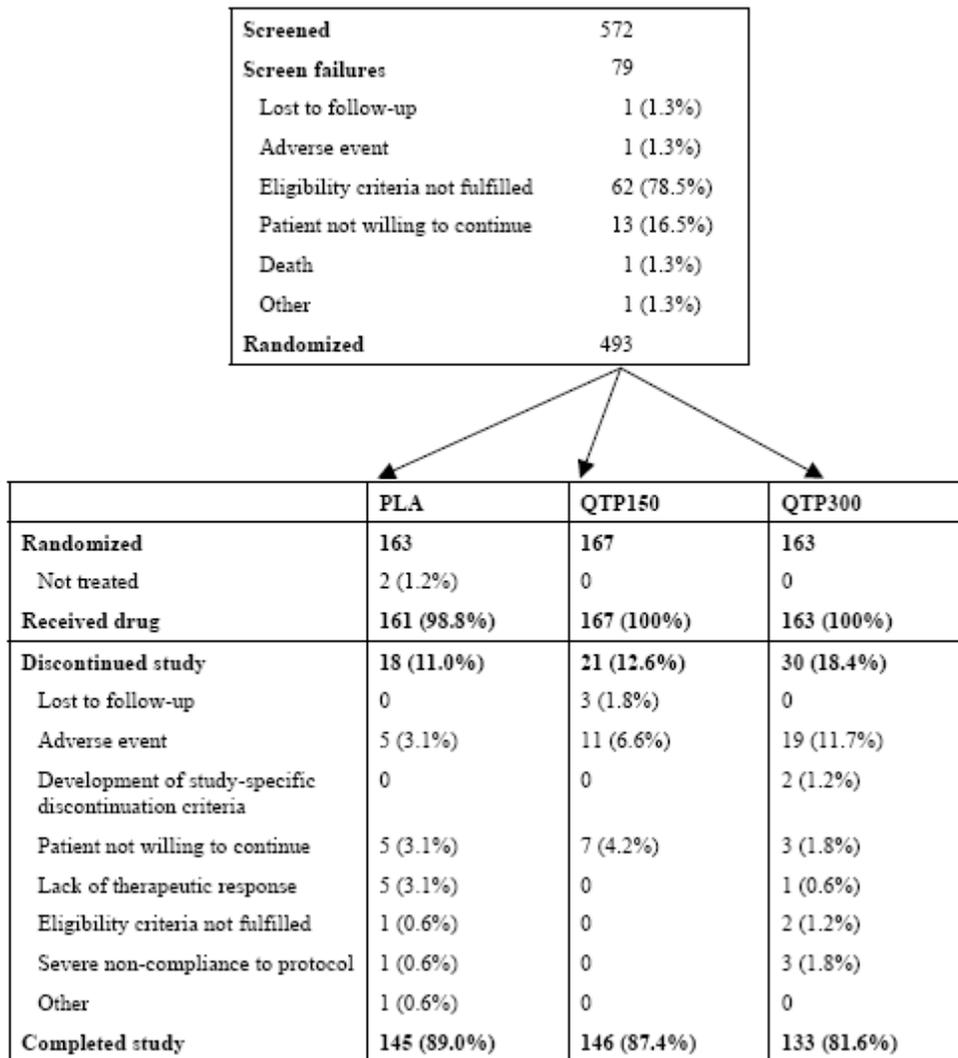
### **Duration of treatment**

Eligible patients underwent a washout period of up to 14 days for the discontinuation of all prohibited medications. Patients then entered a 6-week treatment period, when they were randomly assigned to blinded treatment in a 1:1:1 ratio to 150 mg/day quetiapine XR, 300 mg/day quetiapine XR, or placebo (each in combination with the ongoing antidepressant treatment). All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. Patients in the quetiapine XR 150 mg/day–group maintained this dose through the end of the randomized treatment period. Patients in the quetiapine XR 300 mg/day–group were up-titrated to 300 mg/day on Day 5, and then maintained this dose through the end of the randomized treatment period. The ongoing treatment with the antidepressant was maintained at the same dose throughout the study.

A total of 1854 patients received open-label treatment with quetiapine XR during the open-label phase. Of these, 776 patients continued in the study and received randomized study treatment: 391 received quetiapine XR and 385 received placebo. The mean daily dose of study drug at randomization was similar for the quetiapine XR group (176.6 [95.5] mg) and the placebo group (177.9 [90.8] mg). The mean and median daily doses during the randomized phase did not change considerably from the mean daily dose at randomization. Table 11.3.1.6 summarizes treatment exposure by last open-label dose and confirms that the last dose taken during the open-label phase reflects the mean daily dose of quetiapine XR taken during the randomized phase: 57.1 [27.5] mg for the 50 mg dose group; 154.4 [34.5] mg for the 150 mg dose group; 296.1 [22.1] mg for the 300 mg dose group.

During the open-label phase, mean duration of exposure was 51 days for the open-label only population, 131 days for the patients randomized to placebo, and 131 days for the patients randomized to quetiapine XR. During the randomized phase, mean duration of exposure was higher for the quetiapine XR group (167 days) compared with the placebo group (126 days), which is reflective of the higher rate of discontinuation for the placebo group. Total exposure to study drug over the entire study was 257 days for patients randomized to placebo and 298 days for patients randomized to quetiapine XR. A total of 787 patients completed the open-label phase and received up to 16 weeks of open-label quetiapine XR (Figure 2). A total of 776 patients were randomized to and received either quetiapine XR or placebo. Of the 391 patients who were randomized to receive quetiapine XR, 173 patients received at least 24 weeks of randomized treatment with quetiapine XR, 88 received at least 36 weeks of randomized treatment with quetiapine XR, and 46 received at least 44 weeks of randomized treatment with quetiapine XR.

**Figure 3 Patient disposition (completion or discontinuation)**



PLA Placebo. QTP Quetiapine XR.

In total, 572 patients were screened for possible study participation. Of those, 493 qualified and were assigned to randomized treatment on Day 1. Of the 79 patients who did not qualify, 78.5% (62 patients) were not eligible to receive treatment because eligibility criteria were not fulfilled. Patients who qualified for study entry were assigned to randomized treatment as follows: 163 to placebo, 167 to quetiapine XR 150 mg/day, and 163 to quetiapine XR 300 mg/day.

Overall, the discontinuation rate was highest in the quetiapine XR 300-mg/day group (18.4%) followed by the quetiapine XR 150-mg/day group (12.6%), and the placebo group (11.0%). Discontinuations due to lack of efficacy were more frequent in the placebo group (3.1%) than in any of active treatment groups (0% in the quetiapine XR 150-mg/day group, and 0.6% in the quetiapine XR 300-mg/day group). There was a dose-related increase in the rate of discontinuation due to AEs across the quetiapine XR groups. The rates of discontinuation due

to AEs were higher in the quetiapine XR 150-mg/day group (6.6%) and 300-mg/day group (11.7%) when compared to placebo (3.1%).

Approximately 86% of patients completed the study, with higher rates of completion in the placebo group (89%) in comparison to the quetiapine XR groups (87.4% in the quetiapine XR 150-mg/day group and 81.6% in the quetiapine XR 300-mg/day group).

Quetiapine XR doses of 150 mg/day and 300 mg/day were statistically superior to placebo as demonstrated by the mean change from randomization to Week 6 in the MADRS total score (LOCF, MITT analysis set), with adjustment for multiplicity (quetiapine XR 150 mg vs placebo: p=0.003; quetiapine XR 300 mg vs placebo: p=0.005).

**Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)**

Outcome variable	PLA N=160	QTP150 N=166	QTP300 N=161
MADRS total score, LS mean change from baseline	-12.21	-15.26 <sup>a</sup>	-14.94 <sup>a</sup>
Proportion with ≥50% MADRS response	46.3%	55.4%	57.8% <sup>b</sup>
Proportion with MADRS remission (total score ≤8)	23.8%	36.1% <sup>b</sup>	31.1%
HAM-D total score, LS mean change from baseline	-11.13	-13.81 <sup>c</sup>	-13.56 <sup>a</sup>
HAM-D Item 1 score, LS mean change from baseline	-1.35	-1.56	-1.57
HAM-A total score, LS mean change from baseline	-7.92	-10.27	-9.70
CGI-S score, LS mean change from baseline	-1.25	-1.72 <sup>c</sup>	-1.64 <sup>b</sup>
Proportion improved in CGI-I	52.5%	64.5% <sup>b</sup>	62.7%

**Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)**

Outcome variable	PLA N=160	QTP150 N=166	QTP300 N=161
Q-LES-Q % maximum total score, LS mean change from baseline	12.58	14.70	12.81

<sup>a</sup> p<0.01 comparison with placebo.

<sup>b</sup> p<0.05 comparison with placebo.

<sup>c</sup> p<0.001 comparison with placebo.

CGI-I Clinical Global Impression Improvement scale. CGI-S Clinical Global Impression Severity scale. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. MITT Modified intention-to-treat. PLA Placebo. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR.

Note: For the analyses of MADRS and Q-LES-Q change from baseline, p-values were adjusted and compared with α=0.05 using the Simes-Hommel procedure within the step-wise sequential testing strategy.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

## STUDY 5

### **A Multicenter, Double-blind, Randomized-withdrawal, Parallel-group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended Release (SEROQUEL XR™) as Monotherapy in the Maintenance Treatment of Patients with Major Depressive Disorder Following an Open-Label Stabilization Period (AMETHYST STUDY)**

#### **International co-ordinating Investigator**

Pedro Delgado, MD  
University of Texas  
3939 Medical Drive  
San Antonio, TX 78229

#### **Study centers**

A total of 1876 patients were enrolled

#### **Study design**

This was a multicenter, randomized-withdrawal, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy (time to depressed event) and safety of quetiapine XR for up to 52 weeks of maintenance treatment in adult patients with MDD. The study comprised 4 periods: an enrollment period of up to 28 days; an open-label run-in period of 4 to 8 weeks, an open-label stabilization treatment period of at least 12 weeks (which could have been extended 6 additional weeks to meet eligibility criteria for randomization), and a randomized treatment period of up to 52 weeks.

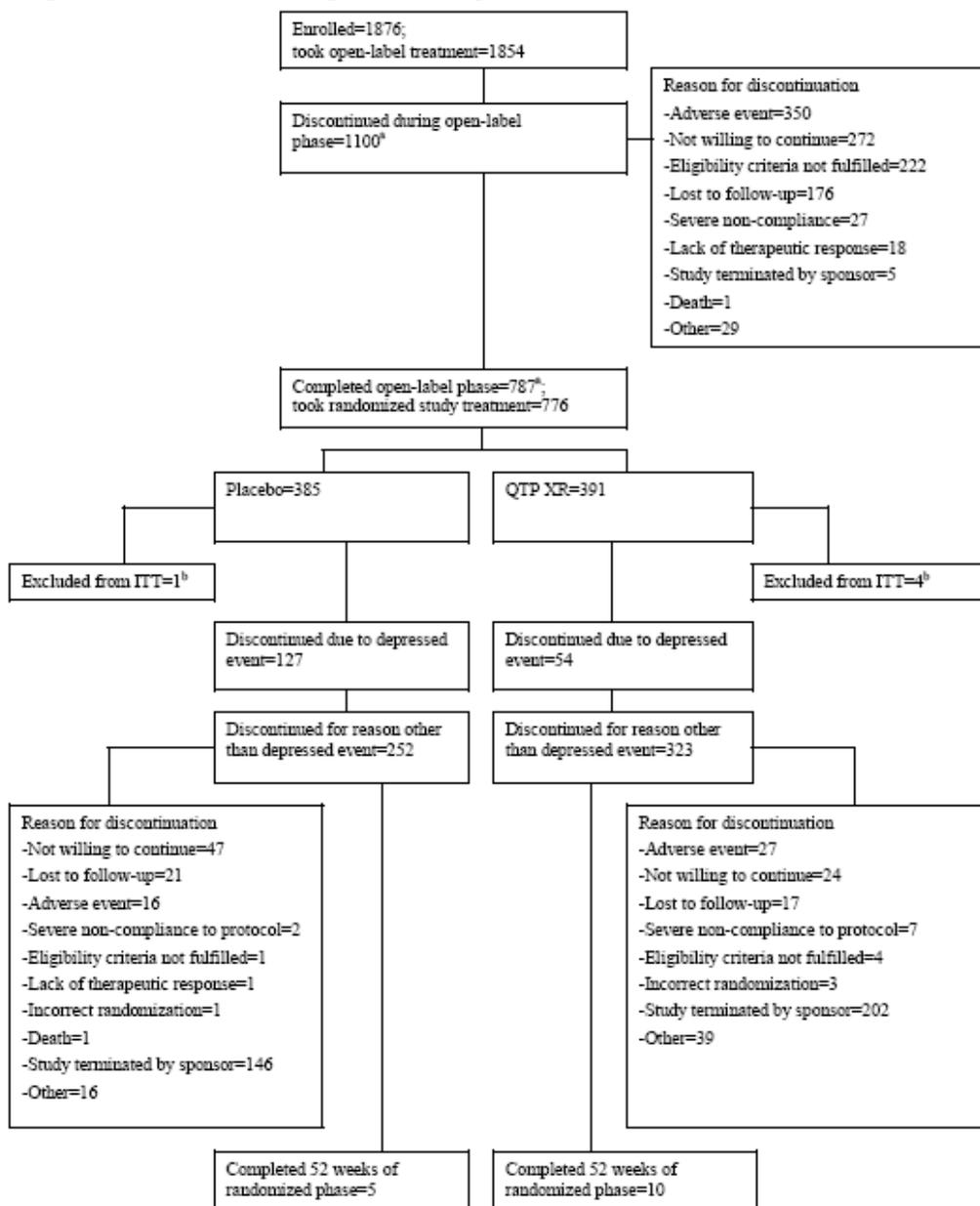
#### **Duration of treatment**

This study consisted of an open-label run-in treatment period of 4 to 8 weeks and an open-label stabilization treatment period of at least 12 weeks (patients were permitted to return to the clinic for up to 3 more visits [ie, for up to 6 more weeks] to meet eligibility criteria for randomization), followed by a randomized treatment period of up to 52 weeks.

A total of 1854 patients received quetiapine XR during the open-label phase of the study; 776 patients received randomized study treatment. The most common reasons for discontinuation during the open-label phase were AE (19%) and not willing to continue (15%). Discontinuations due to a depressed event during randomized treatment were less common in the quetiapine XR group (14%) than in the placebo group (33%). Other than

depressed events and termination of the study by the sponsor, the most frequent reason for discontinuation was AE in the quetiapine XR group (7%) and not willing to continue in the placebo group (12%). During randomized treatment, exposure to study drug was greater in the quetiapine XR group than in the placebo group (167 days vs 126 days). A total of 787 patients completed the open-label phase and received up to 16 weeks of open-label quetiapine XR. A total of 776 patients were randomized to and received either quetiapine XR or placebo. Of the 391 patients who were randomized to receive quetiapine XR, 173 patients received at least 24 weeks of randomized treatment with quetiapine XR, 88 received at least 36 weeks of randomized treatment with quetiapine XR, and 46 received at least 44 weeks of randomized treatment with quetiapine XR.

**Figure 2 Patient disposition (completion or discontinuation)**



<sup>a</sup> This number includes 11 patients who were assigned a randomization number, but did not receive randomized study treatment.

At the time of randomization, patients had been stabilized during an open-label treatment period of at least 12 weeks using the effective quetiapine XR dose range, with 21% receiving 50 mg/day, 46% receiving 150 mg/day, and 32% receiving 300 mg/day.

During the randomized phase, 90% of 91 patients who started at 50 mg/day finished on the same dose, 85% of 170 patients who started on 150 mg/day, and 94% of 130 starting on 300 mg/day finished on their starting dose.

Maintenance treatment with quetiapine XR at flexible doses of 50 mg/day, 150 mg/day, or 300 mg/day statistically significantly increased the time to a depressed event in patients with MDD, with an apparent dose response relationship.

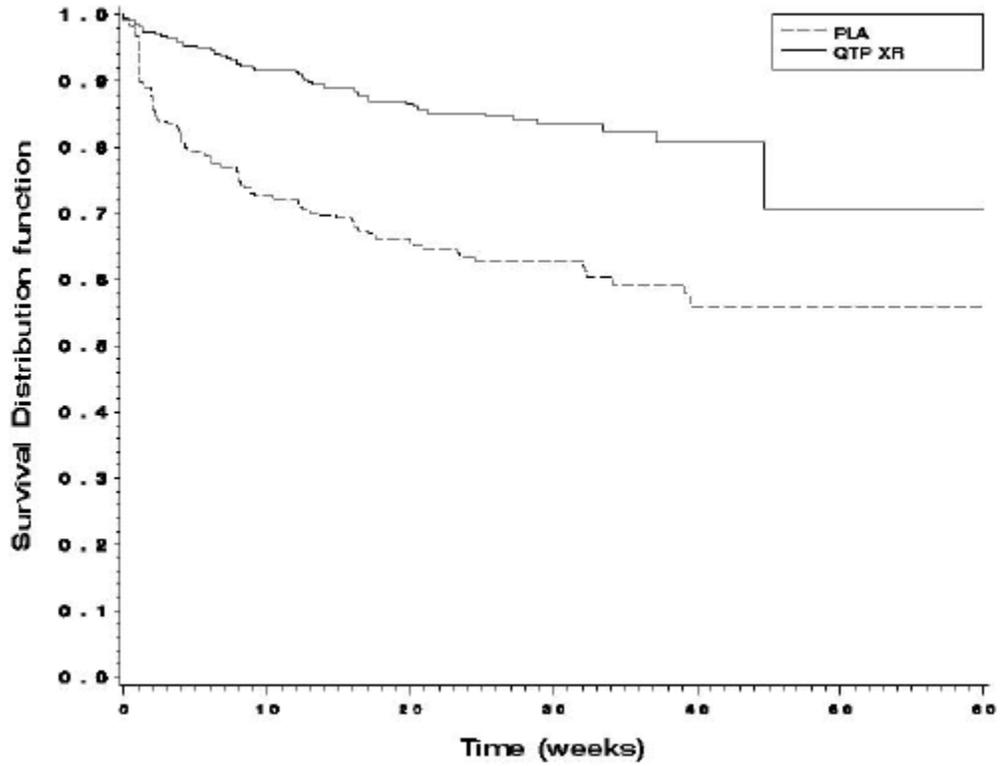
In the maintenance trial (Study 5), a total of 1854 patients received open-label treatment with quetiapine XR during the open label phase. Of these, 776 patients continued in the study and received randomized study treatment: 391 received quetiapine XR and 385 received placebo. The mean daily dose of study drug at randomization was similar for the quetiapine XR group (176.6 [SD=95.5] mg) and the placebo group (177.9 [SD=90.8] mg). Mean duration of exposure was highest for the quetiapine XR group (167 days) compared with the placebo group (126 days) and patients in the open-label phase (51 days), which is reflective of the higher rates of discontinuation for the 2 latter groups. Total exposure during the open-label phase was 151 patient-years. During the randomized phase, total exposure was 133 patientyears for the placebo group and 179 patient-years for the quetiapine XR group. Of the 391 patients who received quetiapine XR in the randomized phase, 173 patients received it for at least 24 weeks, 88 for at least 36 weeks, and 46 for at least 44 weeks.

**Table 36 Overview of exposure**

Analysis set	Open-label only	Randomized safety	
	QTP XR N=1078	PLA N=385	QTP XR N=391
<b>Daily dose at randomization (mg)<sup>a</sup></b>			
N <sup>b</sup>	NA	385	391
Mean (SD)	NA	177.9 (90.8)	176.6 (95.5)
Median	NA	150	150
Min to max	NA	25 to 300	50 to 300
<b>Mean daily dose (mg)<sup>c</sup></b>			
N <sup>b</sup>	1078	385	391
Mean (SD)	151.8 (80.6)	182.1 (91.5)	177.1 (95.6)
Median	143	150	150
Min to max	38 to 628	49 to 300	47 to 300
<b>Median daily dose (mg)<sup>c</sup></b>			
N <sup>b</sup>	1078	385	391
Mean (SD)	159.2 (95.9)	182.6 (92.9)	176.7 (97.4)
Median	150	150	150
Min to max	38 to 300	50 to 300	50 to 300
<b>Minimum daily dose (mg)<sup>c</sup></b>			
N <sup>b</sup>	1078	385	391
Mean (SD)	49.8 (10.4)	172.3 (93.8)	166.9 (98.5)
Median	50	150	150
Min to max	0 to 300	0 to 300	0 to 300
<b>Maximum daily dose (mg)<sup>c</sup></b>			
N <sup>b</sup>	1078	385	391
Mean (SD)	215.0 (333.6)	187.7 (95.0)	186.3 (96.7)
Median	150	150	150
Min to max	50 to 9300	50 to 600	50 to 300
<b>Duration of exposure (days)<sup>c</sup></b>			
N <sup>b</sup>	1078	385	391
Mean (SD)	51.1 (41.8)	126.3 (103.0)	167.0 (103.0)
Median	45	116	158
Min to max	1 to 217	1 to 372	1 to 371
<b>Total exposure (patient-years)</b>	151.1	133.2	178.8

<sup>a</sup> Last prescribed dose during open-label phase.

Figure S1 Time to a depressed event, Kaplan Meier curves (ITT population)



**Table S3 Efficacy results, randomized treatment period (ITT population)**

Outcome variable		PLA	QTP XR	Hazard ratio / estimated difference (95% CI)	p-value
Primary analysis	N	384	387		
Time to depression relapse	Number of relapses (%)	132 (34.4%)	55 (14.2%)	0.34 / (0.25, 0.46) <sup>a</sup>	<0.001 <sup>b</sup>
<b>Secondary analyses</b>					
MADRS total score <sup>c</sup>	LS mean <sup>b</sup> (SE)	2.03 (0.21)	0.15 (0.20)	Diff: 1.88 (0.28) / (1.61, 2.44)	<0.001
CGI-S score <sup>c</sup>	LS mean <sup>b</sup> (SE)	0.23 (0.04)	-0.03 (0.03)	Diff: 0.26 (0.05) / 0.16, 0.35)	<0.001
HAM-A total score <sup>c</sup>	LS mean <sup>b</sup> (SE)	1.58 (0.18)	0.20 (0.17)	Diff: 1.37 (0.25) / (0.89, 1.86)	<0.001
HAM-A psychic anxiety factors score <sup>c</sup>	LS mean <sup>b</sup> (SE)	1.23 (0.12)	0.16 (0.11)	Diff: 1.07 (0.16) / (0.76, 1.38)	<0.001
HAM-A somatic anxiety factors score <sup>c</sup>	LS mean <sup>b</sup> (SE)	0.33 (0.09)	0.06 (0.09)	Diff: 0.27 (0.13) / (0.03, 0.52)	0.031
SDS total score <sup>c</sup>	LS mean <sup>b</sup> (SE)	0.44 (0.28)	-0.45 (0.25)	Diff: 0.89 (0.37) / (0.16, 1.61)	0.016
Q-LES-Q percentage of the maximum total score <sup>c</sup>	LS mean <sup>b</sup> (SE)	-0.36 (0.65)	0.52 (0.59)	Diff: -0.88 (0.86) / (-2.57, 0.80)	0.303
Q-LES-Q Item 15	LS mean <sup>b</sup> (SE)	-0.24 (0.04)	-0.13 (0.04)	Diff: -0.12 (0.06) / (-0.23, -0.01)	0.039
Q-LES-Q Item 16	LS mean <sup>b</sup> (SE)	-0.12 (0.04)	0.02 (0.03)	Diff: -0.14 (0.05) / (-0.23, -0.04)	0.004
PSQI global score <sup>c</sup>	LS mean <sup>b</sup> (SE)	1.35 (0.17)	0.06 (0.15)	Diff: 1.30 (0.22) / (0.87, 1.73)	<0.001

<sup>a</sup> Hazard ratio estimated by Cox proportional hazards model.

<sup>b</sup> Estimate of LS mean change during randomized period from an ANCOVA of the average of all post-baseline measurements from randomization up to, but not including, the relapse; the score at randomization was a covariate, and treatment and region were fixed effects.

<sup>c</sup> Change from randomization

ANCOVA Analysis of covariance. CGI-S Clinical Global Impression-Severity of Illness. CI Confidence interval. HAM-A Hamilton Rating Scale for Anxiety. ITT Intention to treat. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. PLA Placebo. PSQI Pittsburgh Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire. QTP XR Quetiapine extended release. N Number of patients in treatment group. SDS Sheehan Disability Scale. SE Standard error.

Quetiapine XR at flexible doses of 50 mg, 150 mg, or 300 mg significantly increases the time to a depressed event compared with placebo when used as monotherapy in the maintenance treatment of patients with MDD.

I agree with the findings above which are consistent with the FDA statistical reviewer's findings.

#### 6.1.4 Efficacy Findings

Quetiapine XR at doses of 50 mg/day, 150 mg/day, and 300 mg/day was superior to placebo as monotherapy in reducing the level of depressive symptoms through Week 6 or 8 in patients with MDD, as assessed by evaluation of Montgomery-Åsberg Depression Rating Scale (MADRS) total score in studies 1, 2 and 3. Study 4 was not significant..

Quetiapine XR at doses of 150 mg/day and 300 mg/day as adjunct to an antidepressant was superior to antidepressant therapy as adjunct to placebo in reducing the level of depressive symptoms at Week 6 in patients with MDD who had an inadequate response to previous antidepressant treatment, as assessed by evaluation of MADRS total score. See studies 6 and 7. More consistent findings supporting efficacy across primary and secondary variables were noted for the 300 mg/day dose.

Maintenance treatment with quetiapine XR at flexible doses of 50 mg/day, 150 mg/day, or 300 mg/day statistically significantly increased the time to a depressed event in patients with MDD, with an apparent dose response relationship in study 5.

**Table E7 Efficacy results from Studies 1 and 2 at Week 6 (LOCF, MITT analysis set)**

Outcome variable	Study 1				Study 2			
	PLA N=179	QTP 50 N=168	QTP 150 N=179	QTP 300 N=176	PLA N=152	QTP 150 N=147	QTP 300 N=147	DUL N=141
MADRS total score, LS mean change from randomization	-11.07	-13.56c	-14.50b	-14.18b	-11.18	-14.81a	-15.29a	-14.64a
Proportion with MADRS response (total score $\geq$ 50% reduction from randomization)	30.3%	42.7%b	51.2%a	44.9%a	36.2%	54.4%b	55.1%a	49.6%c
Proportion with MADRS remission (total score $\leq$ 8)	18.5%	25.8%	20.8%	26.1%	20.4%	26.5%	32.0%c	31.9%c
HAM-D total score, LS mean change from randomization	-10.93	-12.35	-12.84c	-12.65c	-10.26	-13.12a	-14.02a	-12.37c
HAM-D Item 1, LS mean change from randomization	-1.18	-1.34	-1.45c	-1.48c	-1.07	-1.49a	-1.56a	-1.53a
HAM-A total score, LS mean change from randomization	-6.64	-8.11c	-8.34b	-8.20c	-5.55	-7.76b	-7.38b	-7.83a
CGI-S score, LS mean change from randomization	-1.11	-1.43c	-1.50b	-1.49b	-1.06	-1.43b	-1.60a	-1.53a
Proportion improved on CGI-I	39.3%	52.8%b	54.2%b	54.0%b	39.5%	54.1%c	59.2%a	56.7%b
Q-LES-Q, LS mean change from	12.59	12.50	12.30	11.56	11.26	13.68	13.59	16.69b

randomization

a p<0.001 comparison with placebo b p<0.01 comparison with placebo c p<0.05 comparison with placebo Note: For the analyses of MADRS and Q-LES-Q change from randomization, p-values were adjusted and compared with  $\alpha=0.05$  using the Simes-Hommel procedure within the step-wise sequential testing strategy CGI-I Clinical Global Impression Improvement scale CGI-S Clinical Global Impression Severity scale DUL Duloxetine HAM-A Hamilton Rating Scale for Anxiety HAM-D Hamilton Rating Scale for Depression LS Least square LOCF Last observation carried forward MADRS Montgomery-Asberg Depression Rating Scale MITT Modified intention-to-treat N Number of patients in treatment group PLA Placebo Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire QTP Quetiapine extended release Corresponds to Appendix Table EA001a in Module 5.3.3.3 Pooled Efficacy Data Tables and Table S3 in CSR 1 and Table S3 in CSR 2

**Table E8 Efficacy results from Studies 3 and 4 at Week 8 (LOCF, MITT analysis set)**

Outcome variable	Study 3		PLA N=153	QTP N=154	Study 4 ESC N=152
	PLA N=152	QTP N=147			
MADRS total score, LS mean change from randomization	-13.1	-16.49 <sup>b</sup>	-15.61	-17.21	-16.73
Proportion with MADRS response (total score $\geq 50\%$ reduction from randomization)	48.0%	61.9% <sup>c</sup>	51.0%	60.4%	59.9%
Proportion with MADRS remission (total score $\leq 8$ )	25.0%	34.7% <sup>d</sup>	35.3%	35.7%	40.8%
HAM-D total score, LS mean change from randomization	-12.35	-14.75 <sup>c</sup>	-13.75	-14.99	-14.70
HAM-D Item 1, LS mean change from randomization	-1.40	-1.71 <sup>c</sup>	-1.41	-1.57	-1.65
HAM-A total score, LS mean change from randomization	-7.70	-9.14 <sup>c</sup>	-8.28	-9.44	-9.67
CGI-S score, LS mean change from randomization	-1.24	-1.64 <sup>b</sup>	-1.76	-1.83	-1.85
Proportion improved on CGI-I	52.0%	63.3% <sup>c</sup>	58.8%	61.4%	64.2%
Q-LES-Q, LS mean change from randomization	11.93	13.80	13.55	13.46	16.00

a p<0.001 comparison with placebo b p<0.01 comparison with placebo c p<0.05 comparison with placebo d p=0.052 comparison with placebo Note: For the analyses of MADRS and Q-LES-Q change from randomization, p-values were adjusted and compared with  $\alpha=0.05$  using the Simes-Hommel procedure within the step-wise sequential testing strategy CGI-I Clinical Global Impression Improvement scale CGI-S Clinical Global Impression Severity scale ESC Escitalopram HAM-A Hamilton Rating Scale for Anxiety HAM-D Hamilton Rating Scale for Depression LOCF Last observation carried forward LS Least square MADRS Montgomery-Asberg Depression Rating Scale MITT Modified intention-to-treat N Number of patients in treatment group Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire QTP Quetiapine extended release PLA Placebo Corresponds to Appendix Table EA001b in Module 5.3.5.3 Pooled Efficacy Data Tables, Table S3 in CSR 3, and Table S3 in CSR 4

**Table E9 Efficacy results from Studies 6 and 7 at Week 6 (LOCF, MITT analysis set)**

Outcome variable	Study 6			Study 7		
	PLA N=143	QTP150 N=143	QTP300 N=146	PLA N=160	QTP150 N=166	QTP300 N=161
MADRS total score, LS mean change from randomization	-11.70	-13.60	-14.70 <sup>b</sup>	-12.21	-15.26 <sup>b</sup>	-14.94 <sup>b</sup>
Proportion with MADRS response (total score $\geq 50\%$ reduction from randomization)	46.2%	51.7%	58.9% <sup>c</sup>	46.3%	55.4%	57.8% <sup>c</sup>
Proportion with MADRS remission (total score $\leq 8$ )	24.5%	35.0%	42.5% <sup>b</sup>	23.8%	36.1% <sup>c</sup>	31.1%
HAM-D total score, LS mean change from randomization	-10.80	-12.63 <sup>c</sup>	-13.53 <sup>b</sup>	-11.13	-13.81 <sup>a</sup>	-13.56 <sup>b</sup>
HAM-D Item 1, LS mean change from randomization	-1.35	-1.53	-1.60	-1.35	-1.56	-1.57
HAM-A total score, LS mean change from randomization	-6.67	-7.43	-8.50 <sup>c</sup>	-7.92	-10.27	-9.70
CGI-S score, LS mean change from randomization	-1.23	-1.47	-1.52 <sup>c</sup>	-1.25	-1.72 <sup>a</sup>	-1.64 <sup>c</sup>
Proportion improved on CGI-I	46.9%	58.0%	58.2% <sup>c</sup>	52.5%	64.5% <sup>c</sup>	62.7%
Q-LES-Q, LS mean	11.32	10.37	11.82	12.58	14.70	12.81

change from  
 randomization

a p<0.001 comparison with placebo b p<0.01 comparison with placebo c p<0.05 comparison with placebo Note: For the analyses of MADRS and Q-LES-Q change from randomization, p-values were adjusted and compared with  $\alpha=0.05$  using the Simes-Hommel procedure within the step-wise sequential testing strategy CGI-I Clinical Global Impression Improvement scale CGI-S Clinical Global Impression Severity scale HAM-A Hamilton Rating Scale for Anxiety HAM-D Hamilton Rating Scale for Depression MADRS Montgomery-Asberg Depression Rating Scale N Number of patients in treatment group Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire LOCF Last observation carried forward MITT Modified intention-to-treat LS Least square QTP Quetiapine extended release PLA Placebo Corresponds to Appendix Table EA001c in Module 5.3.5.3 Pooled Efficacy Data Tables, Table S3 in CSR 6, and Table S3 in CSR 7

**Table E10 Efficacy results for Study 5, randomized treatment period (ITT population)**

Outcome variable		PLA	QTP	Hazard ratio (95% CI)	p-value
	N	384	387		
Time to recurrence of a depressed event (all events)	Number of relapses (%)	132 (34.4)	55 (14.2)	0.34 (0.25, 0.46)	<0.0001
Time to recurrence of a late depressed event (randomized >30 days)	Number of relapses (%)	59 (20.7)	39 (11.0)	0.49 (0.32, 0.73)	0.0005

a Hazard ratio estimated by Cox proportional hazards model CI Confidence interval ITT Intention-to-treat PLA Placebo QTP Quetiapine extended release N Number of patients in treatment group

Corresponds to Table 11.2.1.1.1, Section 11.2 in CSR 5.

Phillip Dinh, Ph.D. , the FDA statistical reviewer summarized his findings as follows below.

“All six studies were positive on the primary efficacy variable on at least one dose under investigation. Among five studies that had the key secondary endpoint (Q-LES-Q percent maximum score), none of the studies was positive on the key secondary endpoint. The HAM-A was not a pre-specified endpoint, thus it cannot be used to support labeling claims. Although the numerical evidence suggested that patients who took quetiapine XR benefited from the treatment early in the course of the trials, no appropriate statistical methods were pre-specified to assess this claim formally. Thus the claim that a significant improvement was observed within the first week and continuing throughout the study was not justified

and could only be used descriptively.”

### 6.1.5 Clinical Microbiology

n/a

### 6.1.6 Efficacy Conclusions

I believe Seroquel XR is effective in all 3 indications.

## **7 INTEGRATED REVIEW OF SAFETY**

### **7.1 Methods and Findings**

Patients providing safety information in this clinical trial program included 3337 treated with quetiapine XR and 957 treated with placebo.

#### 7.1.1 Deaths

##### **Acute monotherapy**

There was one death during these studies, Patient E1013573 in Study 2. The patient was a 42-year-old male who died due to homicide (gun shot wound to the chest) on Day 9 of the study.

##### **Acute adjunct therapy**

There were no deaths during the acute adjunct therapy studies (6 and 7).

##### **Maintenance therapy**

Three (0.3%) patients had SAEs leading to death in the open-label phase, and 1 (0.3%) patient in the placebo group had a fatal SAE during the randomized phase. For one patient during the open-label phase, death occurred approximately 2 months after discontinuation from the study.

**Table S 39 Listing of deaths during entire study (Study 5)**

Treatment	Patient No.	Sex/ Age <sup>a</sup> (years)	Treatment duration OLT + RTP (days) <sup>b</sup>	AE (preferred term)	AE (investigators text)	Onset of AE (day) <sup>c</sup>	Causality <sup>d</sup>
<u>Open-label phase</u>							
QTP XR	1018012	F/55	50	Death	Death	63	No
QTP XR	3708006	M/60	23	Metastatic neoplasm	Searing paravertebral tumor	26	No
QTP XR	5407001	M/54	20	Myocardial infarction	Myocardial infarction	21	No
<u>Randomized phase. PLA</u>							

Narratives are provided in the study reports for the following patients: patients who died, patients with serious adverse events, and patients who discontinued treatment because of AEs. I have reviewed the narratives.

### 7.1.2 Other Serious Adverse Events

The incidence of SAEs in the pooled studies is shown below and tended to increase with dose. The most frequently reported non-fatal SAE in the quetiapine XR groups was depression. There are no unusual or unexpected events in this NDA.

**Table S 40 Non-fatal serious adverse events - safety population (Studies 1, 2, 3 and 4)**

System organ class	Preferred term	PLA	ALL QTP	QTP 50	QTP 150	QTP 300
		(N=648)	(N=1149)	(N=181)	(N=595)	(N=373)
		n (%)	n (%)	n (%)	n (%)	n (%)
TOTAL	TOTAL	5 (0.8)	13 (1.1)	1 (0.6)	4 (0.7)	8 (2.1)
Cardiac disorders	TOTAL	1 (0.2)	0	0	0	0
	Angina pectoris	1 (0.2)	0	0	0	0
General disorders and administration site conditions	TOTAL	1 (0.2)	0	0	0	0
	Chest pain	1 (0.2)	0	0	0	0
Hepatobiliary disorders	TOTAL	0	1 (0.1)	0	0	1 (0.3)
	Cholecystitis acute	0	1 (0.1)	0	0	1 (0.3)
Infections and infestations	TOTAL	1 (0.2)	2 (0.2)	1 (0.6)	0	1 (0.3)
	Cellulitis	1 (0.2)	0	0	0	0
	Diverticulitis	0	1 (0.1)	0	0	1 (0.3)
	Pneumonia	0	1 (0.1)	1 (0.6)	0	0
Injury, poisoning and procedural complications	TOTAL	0	2 (0.2)	0	1 (0.2)	1 (0.3)
	Fall	0	1 (0.1)	0	1 (0.2)	0
	Overdose	0	1 (0.1)	0	0	1 (0.3)
Pregnancy, puerperium and perinatal conditions	TOTAL	1 (0.2)	0	0	0	0
	Abortion spontaneous	1 (0.2)	0	0	0	0
Psychiatric disorders	TOTAL	1 (0.2)	8 (0.7)	0	3 (0.5)	5 (1.3)
	Depression	0	6 (0.5)	0	3 (0.5)	3 (0.8)
	Panic attack	0	1 (0.1)	0	0	1 (0.3)
	Suicidal behaviour	0	1 (0.1)	0	0	1 (0.3)
	Suicidal ideation	0	1 (0.1)	0	0	1 (0.3)
	Suicide attempt	1 (0.2)	2 (0.2)	0	1 (0.2)	1 (0.3)

The incidence of SAEs in the adjunct therapy studies was 1.3% in the placebo group and 1.0% in both quetiapine XR groups. The most frequently reported non-fatal SAE was depression.

**Table S 41 Non-fatal serious adverse events - safety population (Studies 6 and 7)**

System organ class	Preferred term	PLA	QTP 150	QTP 300
		(N=309)	(N=315)	(N=312)
		n (%)	n (%)	n (%)
TOTAL	TOTAL	4 (1.3)	3 (1.0)	3 (1.0)
Injury, poisoning and procedural complications	TOTAL	1 (0.3)	1 (0.3)	1 (0.3)
	Drug toxicity	0	0	1 (0.3)
	Fall	0	1 (0.3)	0
	Lower limb fracture	0	1 (0.3)	0
	Overdose	1 (0.3)	0	0
Musculoskeletal and connective tissue disorders	TOTAL	0	1 (0.3)	0
	Spondylitis	0	1 (0.3)	0
Nervous system disorders	TOTAL	1 (0.3)	1 (0.3)	0
	Syncope	0	1 (0.3)	0
	Transient ischaemic attack	1 (0.3)	0	0

**Table S 41 Non-fatal serious adverse events - safety population (Studies 6 and 7)**

System organ class	Preferred term	PLA	QTP 150	QTP 300
		(N=309)	(N=315)	(N=312)
		n (%)	n (%)	n (%)
Psychiatric disorders	TOTAL	3 (1.0)	0	2 (0.6)
	Depression	2 (0.6)	0	2 (0.6)
	Suicide attempt	1 (0.3)	0	0

PLA Placebo. QTP Quetiapine XR.  
 MedDRA Medical Dictionary for Regulatory Affairs, version 10.  
 Corresponds to Table SA020d in Module 5.3.5.3 Pooled Safety Data Tables.

The incidence of non-fatal SAEs during the randomized treatment phase of study 5 was 2.0% and 1.8% in the quetiapine XR and placebo groups, respectively.

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Table 11.3.4.1.1.3 Serious adverse Events not leading to death by Preferred Term  
 Ongoing or during randomized treatment phase  
 Randomized safety analysis set

PREFERRED TERM	ACTUAL TREATMENT GROUP		
	PLA (N=385) n (%)	QTD XR (N=391) n (%)	Total (N=776) n (%)
TOTAL	7 ( 1.8)	8 ( 2.0)	15 ( 1.9)
CHEST PAIN	1 ( 0.3)	0	1 ( 0.1)
CHOLELITHIASIS	0	3 ( 0.8)	3 ( 0.4)
DIVERTICULITIS	0	1 ( 0.3)	1 ( 0.1)
GASTRITIS	0	1 ( 0.3)	1 ( 0.1)
GASTRODUODENITIS	1 ( 0.3)	0	1 ( 0.1)
GASTROENTERITIS	1 ( 0.3)	0	1 ( 0.1)
MENTAL STATUS CHANGES	1 ( 0.3)	0	1 ( 0.1)
MUSCULOSKELETAL CHEST PAIN	1 ( 0.3)	0	1 ( 0.1)
NON-CARDIAC CHEST PAIN	0	1 ( 0.3)	1 ( 0.1)
ESOPHAGEAL FOOD IMPACTION	0	1 ( 0.3)	1 ( 0.1)
REFLUX ESOPHAGITIS	0	1 ( 0.3)	1 ( 0.1)
SUICIDAL IDEATION	1 ( 0.3)	0	1 ( 0.1)
WEST NILE VIRAL INFECTION	1 ( 0.3)	0	1 ( 0.1)

All AEs ongoing at randomization or occurred during randomized treatment phase.

### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Overall profile of dropouts

##### MONOTHERAPY

**Table S 13 Discontinuations - safety population (Studies 1, 2, 3 and 4)**

CATEGORY	PLA (N=648)		ALL QTP (N=1149)		QTP 50 (N=181)		QTP 150 (N=595)		QTP 300 (N=373)	
	n	%	n	%	n	%	n	%	n	%
Total number of randomized patients	648	(100.0)	1149	(100.0)	181	(100.0)	595	(100.0)	373	(100.0)
Completed 6/8 weeks of treatment	486	(75.0)	805	(70.1)	134	(74.0)	404	(67.9)	267	(71.6)
Withdrawals	162	(25.0)	344	(29.9)	47	(26.0)	191	(32.1)	106	(28.4)
--Adverse event	29	(4.5)	164	(14.3)	15	(8.3)	89	(15.0)	60	(16.1)
--Condition under investigation worsened	7	(1.1)	1	(0.1)	0	(0.0)	1	(0.2)	0	(0.0)

**Table S 13 Discontinuations - safety population (Studies 1, 2, 3 and 4)**

CATEGORY	PLA (N=648)		ALL QTP (N=1149)		QTP 50 (N=181)		QTP 150 (N=595)		QTP 300 (N=373)	
	n	%	n	%	n	%	n	%	n	%
--Death	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.2)	0	(0.0)
--Development of study-specific discontinuation criteria	2	(0.3)	6	(0.5)	3	(1.7)	1	(0.2)	2	(0.5)
--Eligibility criteria not fulfilled	2	(0.3)	3	(0.3)	0	(0.0)	3	(0.5)	0	(0.0)
--Lack of therapeutic response	14	(2.2)	11	(1.0)	0	(0.0)	10	(1.7)	1	(0.3)
--Other	8	(1.2)	5	(0.4)	1	(0.6)	2	(0.3)	2	(0.5)
--Severe non-compliance to the CSP	9	(1.4)	22	(1.9)	6	(3.3)	12	(2.0)	4	(1.1)
--Subject did not complete >=50 days study treatment	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
--Subject lost to follow-up	47	(7.3)	66	(5.7)	14	(7.7)	33	(5.5)	19	(5.1)
--Subject not willing to continue study	43	(6.6)	65	(5.7)	8	(4.4)	39	(6.6)	18	(4.8)
Completed TDSS follow-up	346	(53.4)	605	(52.7)	103	(56.9)	298	(50.1)	204	(54.7)
Withdrawals during TDSS follow-up	140	(21.6)	200	(17.4)	31	(17.1)	106	(17.8)	63	(16.9)
--Adverse event	0	(0.0)	6	(0.5)	1	(0.6)	3	(0.5)	2	(0.5)
--Condition under investigation worsened	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
--Development of study-specific discontinuation criteria	1	(0.2)	1	(0.1)	1	(0.6)	0	(0.0)	0	(0.0)
--Eligibility criteria not fulfilled	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.3)
--Lack of therapeutic response	2	(0.3)	1	(0.1)	0	(0.0)	1	(0.2)	0	(0.0)
--Other	5	(0.8)	3	(0.3)	0	(0.0)	3	(0.5)	0	(0.0)
--Severe non-compliance to the CSP	3	(0.5)	5	(0.4)	1	(0.6)	2	(0.3)	2	(0.5)
--Subject did not complete day 14 TDSS assessment	94	(14.5)	115	(10.0)	15	(8.3)	66	(11.1)	34	(9.1)
--Subject lost to follow-up	21	(3.2)	49	(4.3)	10	(5.5)	19	(3.2)	20	(5.4)
--Subject not willing to continue study	13	(2.0)	19	(1.7)	3	(1.7)	12	(2.0)	4	(1.1)

N Number of patients in treatment group. n Number of patients in analysis subgroup. PLA Placebo. QTP Quetiapine XR. Randomized treatment period was 6 weeks for Studies 1 and 2 and 8 weeks for Studies 3 and 4.

The proportion of patients that discontinued from the acute monotherapy studies was greater in the quetiapine XR treatment groups (29.9%) than in the placebo group (25.0%). The

greater number of withdrawals in the quetiapine XR groups can be attributed to the incidences of withdrawal due to adverse events (4.5% in the placebo group and 14.3% in the quetiapine XR groups). There were fewer withdrawals due to adverse events in the 50 mg/day quetiapine group (8.3%) than in the 150 mg/day or 300 mg/day quetiapine groups (15.0% and 16.1%, respectively). The incidence of withdrawal due to ‘condition under investigation worsened’ was 1.1% in the placebo group and 0.1% in the quetiapine XR groups. The other reasons for withdrawal were similar between the placebo and quetiapine XR treatment groups.

## ADJUCTIVE THERAPY

**Table S 14 Discontinuations - safety population (Studies 6 and 7)**

CATEGORY	PLA (N=309)		QTP 150 (N=315)		QTP 300 (N=312)	
	n	%	n	%	n	%
Total number of randomized patients	309	(100.0)	315	(100.0)	312	(100.0)
Completed 6 weeks of treatment	270	(87.4)	260	(82.5)	238	(76.3)
Withdrawals	39	(12.6)	55	(17.5)	74	(23.7)
--Adverse event	6	(1.9)	27	(8.6)	46	(14.7)
--Development of study-specific discontinuation criteria	0	(0.0)	0	(0.0)	2	(0.6)
--Eligibility criteria not fulfilled	0	(0.0)	1	(0.3)	3	(1.0)
--Lack of therapeutic response	9	(2.9)	2	(0.6)	1	(0.3)
--Other	1	(0.3)	0	(0.0)	3	(1.0)
--Severe non-compliance to the CSP	1	(0.3)	2	(0.6)	3	(1.0)
--Subject did not complete >=36 days study treatment	0	(0.0)	1	(0.3)	1	(0.3)
--Subject lost to follow-up	10	(3.2)	11	(3.5)	7	(2.2)
--Subject not willing to continue study	12	(3.9)	11	(3.5)	8	(2.6)
Completed TDSS follow-up	99	(32.0)	92	(29.2)	68	(21.8)
Withdrawals during TDSS follow-up	26	(8.4)	22	(7.0)	37	(11.9)
--Adverse event	0	(0.0)	0	(0.0)	3	(1.0)
--Other	11	(3.6)	9	(2.9)	18	(5.8)
--Severe non-compliance to the CSP	1	(0.3)	1	(0.3)	1	(0.3)
--Subject did not complete day 14 TDSS assessment	6	(1.9)	7	(2.2)	9	(2.9)
--Subject lost to follow-up	3	(1.0)	2	(0.6)	4	(1.3)
--Subject not willing to continue study	5	(1.6)	3	(1.0)	2	(0.6)

N Number of patients in treatment group. n Number of patients in analysis subgroup. PLA Placebo.  
 QTP Quetiapine XR.

The proportion of patients that discontinued from the acute adjunct studies was greater in the quetiapine XR treatment groups (17.5% and 23.7% in the 150 mg/day and 300 mg/day quetiapine XR groups, respectively) than in the placebo group (12.6%). This can be attributed to the increased incidences of withdrawal due to adverse events in the quetiapine XR groups, which increased by dose (1.9% in the placebo group; 8.6% and 14.7% in the 150 mg/day and 300 mg/day quetiapine XR groups, respectively). The incidence of withdrawal due to ‘lack of therapeutic response’ was 2.9% in the placebo group, 0.6% in the 150 mg/day quetiapine XR

group, and 0.3% in the quetiapine XR treatment group. The other reasons for withdrawal were similar between the placebo and quetiapine XR treatment groups.

**Table S 16 Discontinuation from randomized treatment phase (Study 5, ITT population)**

	<b>PLA</b> N=384	<b>QTP</b> N=387
	<b>n (%)</b>	<b>n (%)</b>
Discontinuation due to a depressed event	127 (33.1)	54 (14.0)
Discontinuation due to reason other than depressed event	252 (65.6)	323 (83.5)
-Eligibility criteria not fulfilled	1 (0.3)	4 (1.0)
-Adverse event	16 (4.2)	27 (7.0)
-Lack of therapeutic response	1 (0.3)	0
-Subject not willing to continue	47 (12.2)	24 (6.2)
-Subject lost to follow-up	21 (5.5)	17 (4.4)
-Incorrect randomization	1 (0.3)	3 (0.8)
-Severe non-compliance to protocol	2 (0.5)	7 (1.8)
-Death	1 (0.3)	0
-Terminated by sponsor <sup>a</sup>	146 (38.0)	202 (52.2)
-Other	16 (4.2)	39 (10.1)
Completed randomized treatment phase <sup>b</sup>	5 (1.3)	10 (2.6)

<sup>a</sup> Terminated by sponsor was due to study reaching criterion number of depressed events in entire population.

<sup>b</sup> Treated for up to 52 weeks or not discontinued until study termination.

Note: Patients discontinued due to a depressed event had “Development of study-specific discontinuation criteria” marked in the CRF module for study termination.

ITT Intention-to-treat. PLA Placebo. n Number of patients in analysis set. QTP Quetiapine extended release.

Of the 387 patients in the quetiapine XR group participating in the randomized phase, the most frequent reason for discontinuation (due to a reason other than a depressed event or terminated by sponsor) was “Other” (10.1%), followed by “adverse event (7.0%), and subject not willing to continue (6.2%). Of the 387 patients in the placebo group participating in the randomized phase, the most frequent reason for discontinuation (due to a reason other than a depressed event or terminated by sponsor) was not willing to continue (12.2%), followed by “adverse event and “Other” (both 4.2%). When the required number of depressed events had occurred and the study was terminated by the sponsor, 15 patients had completed the maximum 52 weeks of randomized treatment (10 in the quetiapine XR group and 5 in the placebo group); 348 patients were still participating in the randomized phase (202 patients in the quetiapine XR group and 146 patients in the placebo group).

The number of patients who discontinued due to an adverse events was greater in the quetiapine XR group (27 of the 323 patients not discontinued due to a depressed event) compared to the placebo group (16 of the 252 patients not discontinued due to a depressed

event). However, during the randomized treatment phase, the quetiapine XR group had considerably longer exposure to study drug than the placebo group due to the efficacy of quetiapine in preventing or delaying depressed events. The mean duration of exposure to quetiapine XR was approximately 32% longer (167 days) compared to the exposure to placebo (126 days).

#### 7.1.3.2 Adverse events associated with dropouts

##### **Monotherapy**

In the acute monotherapy pool (Studies 1, 2, 3 & 4), the incidence of AEs leading to discontinuation was higher in quetiapine XR treated patients (14.9%) compared with placebo-treated patients (5.2%). Of the quetiapine XR groups, the incidence of AEs leading to discontinuation was lowest in the 50 mg/day group. Sedation (6.1%), somnolence (2.4%), dizziness (1.1%), and fatigue (1.0%) were the most common AEs leading to discontinuation in quetiapine XR patients.

##### **Adductive therapy**

In the pooled adjunct therapy studies, the incidence of AEs leading to discontinuation was 1.9% in the placebo groups, 8.9% in the 150 mg/day quetiapine XR groups, and 15.4% in the 300 mg/day quetiapine XR groups. Somnolence, sedation, dizziness, and fatigue were the most common reasons for discontinuation in quetiapine XR patients.

##### **Maintenance therapy**

The overall incidence of AEs leading to discontinuation during the open-label treatment phase was 19.8%. The most common AEs leading to discontinuation during the open label phase were somnolence (4.5%), sedation (3.1%), and fatigue (2.0%), most of which were considered drug-related. During the open-label phase, most AEs leading to discontinuation were reported during the first 12 weeks of open-label treatment with quetiapine XR.

The proportion of patients with AEs leading to discontinuation during the randomized phase was comparable for the two treatment groups: 6.4% in the quetiapine XR group and 5.2% in the placebo group.

#### 7.1.4 Other Search Strategies

Safety in special groups defined by sex, age and race was explored by tabulating adverse event incidence by those factors. The incidence of common AEs in patients was generally consistent across gender, age from 18 to 65 and race in both monotherapy and adjunct treatment trials, and did not give rise to any new safety issues regarding the use of quetiapine XR in special groups and situations.

## 7.1.5 Common Adverse Events

### 7.1.5.1 Eliciting adverse events data in the development program

Adverse events were elicited weekly in most studies.

### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The MedDRA-encoded adverse events were appropriate.

### 7.1.5.3 Incidence of common adverse events

The incidence of patients experiencing at least one AE was greater in the quetiapine XR groups (81.7%) than in the placebo group (58.8%). Of the 3 quetiapine XR dose groups, the incidence of common AEs was lowest in the 50 mg/day group.

### 7.1.5.4 Common adverse event tables

The incidence of common AEs is presented below. The incidence increases generally with study drug dose.

**Table S 32 Common adverse events (>=2%) by decreasing incidence - safety population (Studies 1, 2, 3 and 4)**

Preferred term	PLA (N=648)	ALL OTP (N=1149)	OTP 50 (N=181)	OTP 150 (N=595)	OTP 300 (N=373)
	n (%)	n (%)	n (%)	n (%)	n (%)
Dry mouth	53 (8.2)	401 (34.9)	40 (22.1)	214 (36.0)	147 (39.4)
Sedation	29 (4.5)	335 (29.2)	49 (27.1)	167 (28.1)	119 (31.9)
Somnolence	45 (6.9)	286 (24.9)	33 (18.2)	149 (25.0)	104 (27.9)
Dizziness	56 (8.6)	174 (15.1)	16 (8.8)	99 (16.6)	59 (15.8)
Headache	112 (17.3)	175 (15.2)	22 (12.2)	104 (17.5)	49 (13.1)
Nausea	68 (10.5)	128 (11.1)	14 (7.7)	77 (12.9)	37 (9.9)
Constipation	24 (3.7)	96 (8.4)	13 (7.2)	49 (8.2)	34 (9.1)
Fatigue	17 (2.6)	80 (7.0)	11 (6.1)	45 (7.6)	24 (6.4)
Vomiting	14 (2.2)	50 (4.4)	3 (1.7)	27 (4.5)	20 (5.4)
Diarrhoea	47 (7.3)	77 (6.7)	12 (6.6)	46 (7.7)	19 (5.1)
Increased appetite	18 (2.8)	61 (5.3)	8 (4.4)	34 (5.7)	19 (5.1)
Insomnia	53 (8.2)	85 (7.4)	9 (5.0)	57 (9.6)	19 (5.1)
Vision blurred	10 (1.5)	41 (3.6)	3 (1.7)	19 (3.2)	19 (5.1)
Dyspepsia	21 (3.2)	49 (4.3)	4 (2.2)	28 (4.7)	17 (4.6)
Irritability	24 (3.7)	56 (4.9)	11 (6.1)	28 (4.7)	17 (4.6)
Back pain	11 (1.7)	38 (3.3)	3 (1.7)	19 (3.2)	16 (4.3)
Weight increased	3 (0.5)	32 (2.8)	2 (1.1)	16 (2.7)	14 (3.8)
Upper respiratory tract infection	30 (4.6)	31 (2.7)	6 (3.3)	12 (2.0)	13 (3.5)
Anxiety	15 (2.3)	32 (2.8)	2 (1.1)	19 (3.2)	11 (2.9)
Dysarthria	0	14 (1.2)	1 (0.6)	2 (0.3)	11 (2.9)

	PLA (N=648)	ALL QTP (N=1149)	QTP 50 (N=181)	QTP 150 (N=595)	QTP 300 (N=373)
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Myalgia	13 (2.0)	49 (4.3)	8 (4.4)	30 (5.0)	11 (2.9)
Nasal congestion	10 (1.5)	29 (2.5)	1 (0.6)	17 (2.9)	11 (2.9)
Arthralgia	17 (2.6)	37 (3.2)	3 (1.7)	24 (4.0)	10 (2.7)
Musculoskeletal stiffness	7 (1.1)	25 (2.2)	5 (2.8)	10 (1.7)	10 (2.7)
Nasopharyngitis	31 (4.8)	31 (2.7)	3 (1.7)	18 (3.0)	10 (2.7)
Abnormal dreams	11 (1.7)	26 (2.3)	3 (1.7)	15 (2.5)	8 (2.1)
Disturbance in attention	3 (0.5)	18 (1.6)	1 (0.6)	9 (1.5)	8 (2.1)
Pharyngolaryngeal pain	2 (0.3)	22 (1.9)	3 (1.7)	11 (1.8)	8 (2.1)
Sluggishness	3 (0.5)	16 (1.4)	4 (2.2)	4 (0.7)	8 (2.1)
Palpitations	15 (2.3)	20 (1.7)	2 (1.1)	11 (1.8)	7 (1.9)
Asthenia	6 (0.9)	16 (1.4)	7 (3.9)	3 (0.5)	6 (1.6)
Tremor	7 (1.1)	20 (1.7)	5 (2.8)	9 (1.5)	6 (1.6)
Decreased appetite	5 (0.8)	21 (1.8)	3 (1.7)	13 (2.2)	5 (1.3)
Influenza	9 (1.4)	20 (1.7)	3 (1.7)	12 (2.0)	5 (1.3)
Cough	8 (1.2)	18 (1.6)	5 (2.8)	9 (1.5)	4 (1.1)
Hypersomnia	1 (0.2)	18 (1.6)	1 (0.6)	13 (2.2)	4 (1.1)
Abdominal pain upper	11 (1.7)	18 (1.6)	1 (0.6)	14 (2.4)	3 (0.8)
Tachycardia	2 (0.3)	17 (1.5)	1 (0.6)	13 (2.2)	3 (0.8)
Blood pressure increased	2 (0.3)	10 (0.9)	4 (2.2)	5 (0.8)	1 (0.3)

Patients with multiple events falling under the same preferred term are counted only once in that term.

Note: Common AEs: AEs occurring at an incidence of ≥2% in any treatment group.

PLA Placebo. QTP Quetiapine XR.

MedDRA Medical Dictionary for Regulatory Affairs, version 10.

### 7.1.5.5 Identifying common and drug-related adverse events

The incidence of common AEs associated with quetiapine treatment (those observed at an incidence of >2% and at least twice that of placebo) is summarized by treatment for the acute monotherapy pool (Studies 1, 2, 3, & 4) in Table S 34.

**Table S 34 Common adverse events associated with quetiapine XR in patients with MDD - safety population (Studies 1, 2, 3 and 4)**

	PLA (N=648)	ALL QTP (N=1149)	QTP 50 (N=181)	QTP 150 (N=595)	QTP 300 (N=373)
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Dry mouth	53 (8.2)	401 (34.9)	40 (22.1)	214 (36.0)	147 (39.4)
Sedation	29 (4.5)	335 (29.2)	49 (27.1)	167 (28.1)	119 (31.9)
Somnolence	45 (6.9)	286 (24.9)	33 (18.2)	149 (25.0)	104 (27.9)
Constipation	24 (3.7)	96 (8.4)	13 (7.2)	49 (8.2)	34 (9.1)
Fatigue	17 (2.6)	80 (7.0)	11 (6.1)	45 (7.6)	24 (6.4)
Vomiting	14 (2.2)	50 (4.4)	3 (1.7)	27 (4.5)	20 (5.4)

	PLA (N=648)	ALL QTP (N=1149)	QTP 50 (N=181)	QTP 150 (N=595)	QTP 300 (N=373)
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Increased appetite	18 (2.8)	61 (5.3)	8 (4.4)	34 (5.7)	19 (5.1)
Vision blurred	10 (1.5)	41 (3.6)	3 (1.7)	19 (3.2)	19 (5.1)
Myalgia	13 (2.0)	49 (4.3)	8 (4.4)	30 (5.0)	11 (2.9)

MedDRA-encoded adverse events occurring at an incidence of  $\geq 5\%$  in any active treatment group and observed at a rate of at least twice that of placebo. PLA Placebo. QTP Quetiapine XR.

#### 7.1.5.6 Additional analyses and explorations

The uniformity of treatment effects of quetiapine XR in MDD across patient subgroups of sex, race, age and baseline severity of illness were analyzed for change from baseline in MADRS total score at last visit. Differences by geographic region were tabulated for Study 5 and Study 7.

The sponsor's subgroup analysis of pooled data showed that all subgroups changed in the same direction, that no subgroup drove the differences between placebo and quetiapine XR and that no subgroup was excluded from therapeutic effects.

#### 7.1.6 Less Common Adverse Events

#### 7.1.7 Laboratory Findings

As this drug has been reviewed on several previous occasions I will highlight only selected laboratory findings found in this submission.

#### **THYROID:**

#### **MONO**

In the acute monotherapy pool (Studies 1, 2, 3 & 4), thyroid stimulating hormone increased in the quetiapine XR group (0.129 uIU/mL) and decreased in the placebo group (-0.077 uIU/mL). Free thyroxine decreased more in the quetiapine XR group (-0.070 ng/dL) than in the placebo group (-0.015 ng/dL). Free triiodothyronine decreased in the quetiapine XR group (-0.49 pg/mL) and increased in the placebo group (0.18 pg/mL).

#### **ADJUNCTIVE**

In the adjunct therapy studies (Studies 6 & 7), thyroid stimulating hormone increased more in the quetiapine XR groups (0.222 and 0.184 uIU/mL in the 150 mg/day and 300 mg/day

groups, respectively) than in the placebo group (0.077 uIU/mL). Free thyroxine decreased more in the quetiapine XR groups (-0.74 and -0.123 ng/dL in the 150 mg/day and 300 mg/day groups, respectively) than in the placebo group (-0.006 ng/dL). Free triiodothyronine decreased in the quetiapine XR groups (-0.071 and -0.159 pg/mL in the 150 mg/day and 300 mg/day groups, respectively) and increased in the placebo group (0.002 pg/mL).

## **MAINTAINENCE**

During the randomized treatment phase, the mean TSH values decreased in both treatment groups. During the randomised treatment phase, the mean free thyroxine values increased more in the placebo group than in the quetiapine XR group, while the mean free triiodothyronine value increased in the placebo group and decreased in the quetiapine XR group.

In the acute monotherapy pool (Studies 1, 2, 3 & 4), few patients had clinically important thyroid laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

In the acute monotherapy pool (Studies 1, 2, 3 & 4), no patients had both high TSH and low total/free thyroxine shifts to clinically important values at end of treatment

In the adjunct therapy pool (Studies 6 & 7), few patients had clinically important thyroid laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

In the acute adjunct therapy pool (Studies 6 & 7), no patients had both high TSH and low total/free thyroxine shifts to clinically important values at end of treatment

At the end of open-label treatment, no patients in the open-label only population had both a clinically important low free thyroxine value and a clinically important high TSH value. Only 1 patient (in the quetiapine XR group) had both a clinically significant low free thyroxine value and a clinically significant high TSH value at end of treatment. Although hypothyroidism was not reported as an AE for this patient, the clinically significant laboratory values were reported as AEs, as were weight increased and increased appetite. Only 1 patient (in the quetiapine XR group) had a clinically important low free triiodothyronine value and a clinically important high TSH value. This patient had AEs of weight increased and increased appetite. Blood thyroid stimulating hormone increased was also reported as a post-treatment AE (occurring within 30 days of last dose of study drug). No major differences between randomized treatment groups were observed.

## **Hematology:**

In the acute monotherapy pool (Studies 1, 2, 3 & 4), there were no clinically relevant differences in mean change from randomization between treatment groups for any hematology assessments.

In the adjunct therapy pool (Studies 6 & 7), there were no clinically relevant differences in mean change from randomization between treatment groups for any hematology assessments.

In the acute monotherapy pool (Studies 1, 2, 3 & 4), few patients had clinically important hematology laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

In the acute adjunct therapy pool (Studies 6 & 7), few patients had clinically important hematology laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

In the maintenance (Study 5), few patients had clinically important hematology laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

### **Leukocytes:**

In the acute monotherapy pool (Studies 1, 2, 3 & 4) there were no clinically relevant differences in mean change from randomization between treatment groups for any leukocyte differential assessments.

In the acute adjunct therapy pool (Studies 6 & 7) there were no clinically relevant differences in mean change from randomization between treatment groups for any leukocyte differential assessments.

In Study 5, there were no remarkable changes in mean leukocyte differential parameters during the open-label treatment phase. Also, there were no clear systematic differences in mean change from randomization between treatment groups for any leukocyte differential parameters.

In the acute monotherapy pool (Studies 1, 2, 3 & 4), few patients had clinically important leukocyte differential laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

In the adjunct therapy pool (Studies 6 & 7), few patients had clinically important leukocyte differential laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

In the maintenance study (Study 5), few patients had clinically important leukocyte differential laboratory values, and there were no differences across the treatment groups that were judged to be clinically relevant.

**Table S 69 Leukocyte shifts to clinical importance at any time - safety population (Studies 1, 2, 3 and 4)**

PLA (N=648)	ALL QTP (N=1149)			QTP 50 (N=181)			QTP 150 (N=595)			QTP 300 (N=373)					
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)			
Basophils, (109 cells/L)															
≥0.5 x 10E9 cells/L	578	0	(0.0)	1005	0	(0.0)	156	0	(0.0)	524	0	(0.0)	325	0	(0.0)
Eosinophils, (109 cells/L)															
≥1x10E9 cells/L	577	0	(0.0)	1003	3	(0.3)	155	0	(0.0)	523	3	(0.6)	325	0	(0.0)
Leucocytes, (109 cells/L)															
≤3 x 109 cells/L	578	3	(0.5)	1009	7	(0.7)	156	1	(0.6)	525	4	(0.8)	328	2	(0.6)
≥16 x 109 cells/L	578	0	(0.0)	1008	5	(0.5)	155	0	(0.0)	525	4	(0.8)	328	1	(0.3)
Lymphocytes, (109 cells/L)															
≤0.5 x 109 cells/L	577	1	(0.2)	1004	0	(0.0)	155	0	(0.0)	524	0	(0.0)	325	0	(0.0)
≥6 x 109 cells/L	578	0	(0.0)	1005	0	(0.0)	156	0	(0.0)	524	0	(0.0)	325	0	(0.0)
Monocytes, (109 cells/L)															
≥1.4 x 109 cells/L	578	0	(0.0)	1005	3	(0.3)	156	0	(0.0)	524	3	(0.6)	325	0	(0.0)
Neutrophils, (109 cells/L)															
<0.5 x 109 cells/L	578	0	(0.0)	1005	0	(0.0)	156	0	(0.0)	524	0	(0.0)	325	0	(0.0)
≥10 x 109 cells/L	576	7	(1.2)	999	1	(1.1)	154	0	(0.0)	523	9	(1.7)	322	2	(0.6)
Neutrophils, (109 cells/L)															
<1.5 x 109 cells/L	578	12	(2.1)	1005	2	(2.3)	156	4	(2.6)	524	1	(2.1)	325	8	(2.5)
≥10 x 109 cells/L	576	7	(1.2)	999	1	(1.1)	154	0	(0.0)	523	9	(1.7)	322	2	(0.6)

N is number of patients at risk, i.e. not fulfilling the criteria at randomization. PLA Placebo. QTP Quetiapine XR.

**MONOTHERAPY**

The incidence of AEs potentially associated with neutropenia and agranulocytosis was 0.0% in the placebo group and 0.2% in the quetiapine XR group. The 2 AEs potentially associated with neutropenia and agranulocytosis occurred in studies 2 and 3.

In Study 2, a non-serious AE (neutrophil count decreased) associated with neutropenia or agranulocytosis was reported for 1 patient in the 150 mg/day quetiapine XR group (Patient E1040517). This patient had an AE of neutrophil count decreased, with a neutrophil particle concentration of  $4.20 \times 10^9$  cells/L at baseline (Visit 1) and  $1.12 \times 10^9$  cells/L at Week 4. The event was considered by the investigator to be drug-related, although no action was taken with regard to study drug. Neutrophil particle concentration increased to  $4.88 \times 10^9$  cells/L at an unscheduled visit at Week 4 and remained normal at Week 6 (End of Treatment) ( $3.76 \times 10^9$  cells/L) (see Tables 11.3.6.2.5 in Study 2 CSR and 11.3.7.2.1.4 in Study 2 CSR). There were no AEs related to agranulocytosis.

In Study 3, a non-serious AE (neutropenia) associated with neutropenia or agranulocytosis was reported for 1 patient in the quetiapine XR group (Patient E1099220). This patient had a low neutrophil count (not clinically important) at randomization ( $1.69 \times 10^9$ /L), which decreased to  $1.11 \times 10^9$ /L by Week 4 and  $0.75 \times 10^9$ /L at an unscheduled visit. At the scheduled Week 8 visit (End of Treatment), values had increased to  $1.54 \times 10^9$ /L. Overall, there were 3 placebo patients and 4 quetiapine XR patients with shifts to clinically important low neutrophil values at the end of treatment.

There were no cases of agranulocytosis.

#### ADJUNCTIVE THERAPY:

There were only two AEs potentially associated with neutropenia and agranulocytosis, both in the quetiapine XR 150 mg/day group.

In Study 6, there was 1 AE (neutropenia) associated with neutropenia or agranulocytosis. This event was reported on Day 28 (Week 4) in a patient in the quetiapine XR 150 mg/day group (Patient E1338403). The patient had a normal neutrophil value at baseline ( $4.21 \times 10^9$ /L) and a potentially clinically important low value at Week 4 ( $0.82 \times 10^9$ /L). A repeat measurement taken 15 days after Week 4 (but 5 days before the Week 6 visit) showed a neutrophil value of  $0.64 \times 10^9$ /L. The neutrophil level had returned to normal at Week 6 of randomized treatment ( $2.05 \times 10^9$ /L). The patient's WBC count was normal at baseline and at Week 6 ( $7.2 \times 10^9$ /L and  $4.4 \times 10^9$ /L, respectively), but was below the lower limit of normal at Week 4 ( $3.9 \times 10^9$ /L). The AE of neutropenia was of moderate intensity and was not an SAE, but it did result in the discontinuation of the patient from the study and was considered by the investigator to be possibly related to study medication. The other AEs reported for this patient were headache, constipation, dysphagia, nausea, fatigue, and vomiting.

In Study 7, there was 1 AE (neutrophil count decreased) associated with neutropenia or agranulocytosis. This event occurred in a patient in the quetiapine XR 150 mg/day group (Patient E3005406); the investigator noted that the percent neutrophils was 23.4% at Week 4

(normal range, 40.9% to 77.0%). The patient had a normal neutrophil value at baseline ( $2.50 \times 10^9$  cells/L) and a potentially clinically low value at Week 4 ( $1.36 \times 10^9$  cells/L). The neutrophil level had returned to normal at Week 6 of randomized treatment ( $2.36 \times 10^9$ /L). The patient's WBC counts were normal at baseline, Week 4, and the end of treatment ( $6.4 \times 10^9$  cells/L,  $5.8 \times 10^9$  cells/L, and  $7.3 \times 10^9$  cells/L, respectively). An AE of sinusitis was reported for this patient 4 days after the Week 4 visit. The AE of neutrophil count decreased was of moderate intensity, was not an SAE, did not result in discontinuation of the patient from the study, and was not considered by the investigator to be possibly related to study medication.

There were no cases of agranulocytosis.

#### MAINTAINENCE THERAPY:

There were no cases of agranulocytosis reported during the open-label phase. The incidence of AEs potentially related to neutropenia or agranulocytosis was low (0.4%). AEs included neutrophil count decreased (0.3%) and neutropenia (0.1%). No patients discontinued due to an AE potentially related to neutropenia during the open-label phase. None of the AEs potentially related to neutropenia and agranulocytosis reported during the open-label phase were considered serious. Most AEs potentially related to neutropenia and agranulocytosis were considered mild or moderate in intensity, and most were considered drug-related.

There were no cases of agranulocytosis reported during the randomized phase phase. The incidence of AEs potentially related to neutropenia was low overall: 0.3% in the placebo group and 0 patients in the quetiapine XR group. During the randomized phase, only 1 patient in the placebo group reported neutrophil count decreased, which occurred during the first week of study treatment; the AE was not serious and it was moderate in intensity. No patients discontinued due to an AE potentially related to neutropenia.

#### **EPS:**

##### MONO

The incidence of AEs potentially associated with EPS was 3.2% in the placebo group and 5.4% in the quetiapine XR groups. Tremor (1.7%), restlessness (1.3%), and akathisia (1.3%) accounted for the majority of reports in the quetiapine XR groups.

All but 2 of the AEs associated with EPS in quetiapine-treated patients were either mild or moderate in intensity. The 2 severe AEs were coded under the preferred term 'restlessness'.

None of the AEs potentially associated with EPS were considered an SAE. Discontinuation due to an AE potentially associated with EPS was reported for 4 patients in the quetiapine XR groups (3 in the 150 mg/day group and 1 in the 300 mg/day group) and no patients in the placebo group. The median day of onset was Day 5 in the quetiapine XR groups and Day 16

in the placebo group.

## ADJUCTIVE

The incidence of AEs potentially associated with EPS was 4.2% in the placebo group, 3.8% in the quetiapine XR 150 mg/day group, and 6.4% in the quetiapine XR 300 mg/day group. Akathisia, restlessness, and tremor accounted for most of the reports in the quetiapine XR groups.

All but 2 of the AEs associated with EPS in quetiapine-treated patients were either mild or moderate in severity, and there was no clinically important differences in severity of EPS-associated AEs across treatments.

None of the AEs potentially associated with EPS were considered an SAE. Discontinuation due to an AE potentially associated with EPS was reported for 3 patients in the quetiapine XR groups and zero patients in the placebo group. The median day of onset was Day 8 in the quetiapine XR groups and Day 17 in the placebo group.

## Maintenance therapy

The incidence of AEs potentially related to EPS during the open-label phase was 6.7%. The most frequent AEs during the open-label phase were restlessness (2.1%), extrapyramidal disorder and tremor (1.5% for both AEs), and akathisia (1.2%). A small proportion of patients discontinued the study due to AEs potentially related to EPS: extrapyramidal disorder (0.3%), akathisia (0.2%), and restlessness (0.1%). AEs potentially related to EPS during the open label phase occurred within the first 12 weeks of open-label treatment and incidences generally decreased during that time.

None of the AEs potentially related to EPS reported during the open-label phase were considered serious. Most AEs potentially related to EPS were considered mild or moderate in intensity, and most were considered drug-related.

During the randomized phase, the incidence of AEs potentially related to EPS was low in both the quetiapine XR group (2.8%) and the placebo group (1.8%). The most frequent AEs reported for the quetiapine XR group during the randomized phase were extrapyramidal disorder (0.8%), tremor (0.8%), and restlessness (0.5%), all of which had an incidence comparable to placebo (0.5%, 0.3%, and 1.0%, respectively). No patients discontinued the study due to AEs potentially related to EPS during the randomized phase.

None of the AEs potentially related to EPS reported during the randomized phase were considered serious. Most AEs potentially related to EPS were considered mild or moderate in intensity, and most were considered drug-related.

## SEXUAL ADVERSE EVENTS:

MONO

The incidence of AEs potentially associated with sexual dysfunction was 1.2% in the placebo group and 1.4% in the quetiapine XR group.

In study 2 the results were as follows.

The incidence of AEs potentially related to sexual dysfunction was low in both quetiapine XR groups and comparable to placebo (1.3% in all 3 groups). The incidence was higher in the duloxetine group (8.1%); these events occurred primarily in males. Based on the change from baseline to the end of treatment in the CFSQ total score, sexual functioning improved slightly in all 4 treatment groups, with no apparent difference between the groups.

In study 4 the results were as follows.

The overall incidence of AEs relating to sexual dysfunction was low (<3%) but tended to occur more often in the escitalopram and placebo groups (2.6% and 1.9%, respectively) than in the quetiapine XR group. The number of events was small in this study. See below.

**Table 49 Adverse events potentially related to sexual dysfunction (safety analysis set)**

	<b>PLA</b> N=155	<b>QTP</b> N=157	<b>ESC</b> N=156
<b>MedDRA preferred term<sup>a</sup></b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
<b>Total</b>	3 (1.9)	1 (0.6)	4 (2.6)
Erectile dysfunction	1 (0.6)	1 (0.6)	0
Libido decreased	1 (0.6)	0	2 (1.3)
Anorgasmia	0	0	1 (0.6)
Ejaculation failure	0	0	1 (0.6)
Loss of libido	1 (0.6)	0	0

<sup>a</sup> Patients with multiple events falling under the same preferred term are counted only once in that term.  
 ESC Escitalopram. MedDRA Medical Dictionary for Regulatory Activities. n Number of patients. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine XR.

ADJUNCTIVE

The incidence of AEs associated with sexual dysfunction was 0.3% in the placebo group, 0.3% in the quetiapine XR 150 mg/day group, and 1.6% in the quetiapine XR 300 mg group.

Maintenance:

The incidence of AEs potentially related to sexual dysfunction during the open-label phase

was low (1.2%). No AEs potentially related to sexual dysfunction resulted in discontinuation from the study. None of the AEs were considered serious, most were considered mild or moderate in intensity, and most were considered drugrelated.

During the randomized phase, the incidence of AEs potentially related to sexual dysfunction was slightly higher for the quetiapine XR group (1.5%) compared with the placebo group (0.5%). None of the AEs resulted in discontinuation from the study, none were considered serious, and most were considered mild or moderate in intensity. Most of the AEs reported for the quetiapine XR group were considered drugrelated, but neither of the 2 AEs reported for the placebo group were considered drug-related.

## **WEIGHT:**

### **Acute monotherapy**

The incidence of patients showing a weight gain from baseline of  $\geq 7\%$  of body weight was 2.4% in the placebo group, 1.1% in the quetiapine XR 50 mg/day group, 3.8% in the quetiapine XR 150 mg/day group, and 5.5% in the quetiapine XR 300 mg/day group.

### **Acute adjunct therapy**

The incidence of patients showing a weight gain from baseline of  $\geq 7\%$  of body weight was 1.7% in the placebo group, 3.2% in the quetiapine XR 150 mg/day group, and 7.2% in the quetiapine XR 300 mg/day group.

### **Maintenance therapy**

The incidence of patients showing a weight gain of  $\geq 7\%$  of body weight during prolonged exposure (randomization phase) was 2.9% in the placebo group and 5.4% in the quetiapine XR group.

#### **7.1.10 Immunogenicity**

n/a

#### **7.1.11 Human Carcinogenicity**

n/a

### 7.1.12 Special Safety Studies

#### **SUICIDALITY**

There have been 3 previous Columbia-type analyses of suicidality in quetiapine studies: 1 for the use of quetiapine in the treatment of bipolar depression, 1 for the use of quetiapine XR in the treatment of schizophrenia, and 1 for the use of quetiapine in the treatment of bipolar maintenance. In these previous reports, quetiapine exhibited no tendency to increase suicidal behavior or ideation in adults with bipolar disorder (at doses of 300 mg to 600 mg once daily) or in adults with schizophrenia (at daily doses of 300 mg to 800 mg).

AstraZeneca conducted an in-house review of suicidal behavior and ideation in the 7 studies in the quetiapine XR MDD treatment program, following the process developed by the group at Columbia University under the leadership of Kelly Posner PhD. A group of AstraZeneca medical staff trained in psychiatry, but not associated with the 7 studies in this program, was identified to review the adverse events (AEs) for patients from these studies. These reviewers were trained in the Columbia review process and were apprised of the reconciliation process to be used in the event of discordant categorization of a particular patient with possible suicidal behavior by the 3 reviewers involved; the 3 reviewers were required to come to agreement on all cases. All study data were blinded to the reviewers.

Analysis of suicidality according to the Columbia method revealed relative risk estimates for quetiapine XR 50, 150 and 300 mg that were not statistically separable from placebo. The adjusted risk ratio for all patients in Studies 1, 2, 3, 4, 6 and 7 who were treated with quetiapine XR compared to those treated with placebo was 0.84 (95% CI: 0.36, 1.97) for events classified as suicidal behavior/ideation, and risk ratios for individual quetiapine XR treatment groups in the data pool ranged from 0.40 to 0.88, with confidence intervals that included the value 1.0. The incidence of AEs classified as suicidality was low and similar across treatment groups.

In these studies of patients with MDD, there was no increased risk of suicidal behavior or ideation with the administration of quetiapine XR at doses of 50 mg to 300 mg daily, compared with the administration of placebo, when used in the treatment of MDD as monotherapy or adjunct therapy.

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Overall, abrupt treatment discontinuation led to an increase in the incidence and/or intensity of a spectrum of signs and symptoms. The most prominent effects were seen for the symptoms of vomiting, nausea, headache, diarrhea, insomnia, irritability, and dizziness, regardless of the length of previous exposure to quetiapine XR treatment.

#### 7.1.14 Human Reproduction and Pregnancy Data

In order to capture and report all cases of pregnancy that occurred during treatment with quetiapine XR (including those not reported as AEs or SAEs), the Clintrace database was searched covering all 7 studies (1, 2, 3, 4, 5, 6 & 7) for all pregnancy cases reported during these studies in which patients were treated with quetiapine XR.

All of the patients with pregnancies reported during study treatment had negative serum pregnancy tests at enrollment as required by the study inclusion criteria. To qualify for enrollment, female patients of childbearing potential were required to use a reliable method of contraception, such as hormonal contraceptives (eg, oral contraceptive or long-term injectable or implantable hormonal contraceptive), double-barrier methods (eg, condom and diaphragm, condom and foam, condom and sponge), intrauterine devices, or tubal ligation. The use of hormonal contraceptives was recorded as concomitant medication.

There was one pregnancy in acute adjunct therapy Study 7. The patient was assigned the 300 mg/day quetiapine XR group. The pregnancy was terminated by elective abortion. There were eight pregnancies in the maintenance study. A majority of the pregnancies lead to timely delivery of healthy babies or elective abortions. One patient delivered a full-term baby with possible congenital bladder abnormality. This event was captured as a post-treatment SAE.

#### 7.1.15 Assessment of Effect on Growth

N/A

#### 7.1.16 Overdose Experience

There were no cases of overdose with quetiapine XR in any of the acute monotherapy studies.

There were no cases of overdose with quetiapine XR in any of the acute adjunct studies.

In the maintenance study (Study 5), a total of 15 patients had a reported overdose during the study that involved, or was suspected to involve, quetiapine XR. There were no reports of completed suicide associated with quetiapine XR overdose during the study. Of the 15 reported overdoses, 5 were considered intentional overdoses and/or suicide attempts, 5 were considered accidental overdoses, and 8 were considered possible overdoses. The maximum single quetiapine XR dose reported was 9300 mg; the patient recovered without sequelae. Five reports of overdose were considered to be SAEs or were associated with SAEs; 10 reports were considered to be, or were associated with, nonserious AEs.

#### 7.1.17 Postmarketing Experience

Patient-years of SEROQUEL use has been calculated from the number of tablets delivered to

wholesalers worldwide during the PSUR period. A daily dose of 300 to 450 mg/patient/day has been assumed based upon a one-year exposure. There have been an estimated 2,035,069 to 1,356,713 patient-years (respectively) of SEROQUEL use during this reporting period, based on those average daily doses.

It has been estimated that about 25.9 million patients worldwide (an estimate of almost 15.9 million patients in the United States (US) and 10 million patients outside the US) have been exposed to SEROQUEL since launch through 31 July 2007 for the US and through second quarter 2007 for countries outside the US.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

#### 7.2.1.1 Study type and design/patient enumeration

**Table S 5 Safety population data sets**

<b>Data Pool</b>	<b>Studies Included</b>	<b>Number of Patients treated with Quetiapine XR</b>
Acute monotherapy pool	Studies 1, 2, 3 and 4	1149
Acute fixed-dose monotherapy pool	Studies 1 and 2	840
Acute modified fixed-dose monotherapy pool	Studies 3 and 4	309
Acute adjunct therapy pool	Studies 6 and 7	627
Maintenance study	Study 5	1854

#### 7.2.1.2 Demographics

##### MONO

The populations of Study 1 and Study 2 were similar with respect to their demographic profiles. Females constituted more than half of the MITT population (51.0% to 64.5% across treatment groups) in the 2 studies. The mean age was closely matched between the studies (range from 40.2 to 42.3 years). Most of the population of both studies was Caucasian (range from 69.1% to 76.4%), and 17.7% to 25.7% were Black. The majority of patients in both studies were in the overweight to obese categories at screening (BMI  $\geq$ 25).

Both study 3 and 4 populations were similar with respect to their demographic profiles. Females were the majority of the MITT population (range from 64.5% to 75.7% across the treatment groups) in the 2 studies. The mean age was closely matched between the studies (range from approximately 39.7 to 43.3 years). The majority of patients in both studies were Caucasian (range from 52.6% to 68.7%), and 13.0% to 27.6% were Black.

## ADJUCTIVE

The majority of patients across both studies 6 and 7 were diagnosed as having recurrent MDD, but the percentage of patients with recurrent MDD was higher in Study 6 (90.4% to 94.4%) than in Study 7 (80.6% to 82.0%). The mean number of previous depressed episodes over lifetime was higher among patients in Study 6 (13.0 to 14.0) than did patients in Study 7 (11.8 to 17.8). In Study 3, a total of 46.7% to 53.7% of patients had family members with a known diagnosis of MDD, compared with only 34.3% to 42.5% of patients in Study 4. Mean MADRS total scores ranged from 27.2 to 28.6 points across treatment groups in the 2 studies. A minor difference between studies was that the percentage of patients with a HAM D total score  $\geq 28$  at randomization was lower in Study 6 than in Study 7 (11.6 to 15.4 points in Study 6 and 18.7 to 21.1 points in Study 7).

## MAINTAINANCE

The majority of study 5 patients in the 2 treatment groups were diagnosed as having recurrent MDD, (83.3% and 86.8% for placebo and quetiapine XR, respectively). The mean number of previous depressed episodes over lifetime was similar for the 2 treatment groups (9.0 and 10.2 for placebo and quetiapine XR, respectively). A similar percentage of patients in the 2 treatment groups had family members with a known diagnosis of MDD (51.8% and 48.6% for placebo and quetiapine XR, respectively). Mean MADRS total scores were 5.3 for the placebo group and 5.8 for the quetiapine XR group.

### 7.2.1.3 Extent of exposure (dose/duration)

This Summary of Clinical Safety provides an integrated view of the safety data from the clinical program for quetiapine XR in MDD. The program comprised 7 studies and included 5933 patients with MDD, of whom 4086 were treated with quetiapine XR. There were 2116 MDD patients assigned to randomized treatment in 4 Phase III acute monotherapy studies (Studies 1, 2, 3, and 4), of whom 1149 received quetiapine XR. There were 939 MDD patients assigned to randomized treatment in 2 Phase III acute adjunct therapy studies (Studies 6 and 7), of whom 627 received quetiapine XR. Moreover, the clinical program included a Phase III maintenance therapy study (Study 5) which exposed 1854 MDD patients to quetiapine XR during the open-label phase.

**Table O 6 Total exposure to quetiapine XR for the combined data of Studies 1, 2, 3 and 4 (safety population)**

	Studies 1 + 2 + 3 + 4				
	PLA N=648	All QTP XR N=1149	QTP XR 50 mg N=181	QTP XR 150 mg N=595	QTP XR 300 mg N=373
Duration of exposure (days) <sup>a</sup>					
Mean (SD)	44.4 (16.9)	39.4 (17.4)	35.9 (12.9)	40.5 (19.2)	39.2 (16.1)
Median	49	43	42	44	43
Min	1	1	1	1	1
Max	77	73	49	73	65
Total exposure (patient-years <sup>b</sup> )	78.8	123.6	17.7	66.0	40.0
Compliance during randomized phase					
≥80% and ≤120%	631 (97.4)	1107 (96.3)	173 (95.6)	573 (96.3)	361 (96.8)
<80%	10 (1.5)	28 (2.4)	7 (3.9)	15 (2.5)	6 (1.6)
>120%	7 (1.1)	14 (1.2)	1 (0.6)	7 (1.2)	6 (1.6)

<sup>a</sup> Does not include treatment withdrawal period.

<sup>b</sup> Includes treatment withdrawal period.

Refer to [Section 1.2 in 2.7.4 Summary of Clinical Safety, Module 2](#)

N Number of patients in dose group. n Number of patients in analysis subgroup. PLA Placebo. QTP XR Quetiapine XR.

Study 1 Study D1448C00001. Study 2 Study D1448C00002. Study 3 Study D1448C00003.

Study 4 Study D1448C00004.

Note: Patient-years defined as the sum of the duration of exposure across patients in days divided by 365.

**Table O 7 Total exposure to quetiapine XR as an adjunct to antidepressants for the combined data of Studies 6 and 7 (safety population)**

	Studies 6 + 7		
	PLA N=309	QTP XR 150 mg N=315	QTP XR 300 mg N=312
Duration of exposure (days) <sup>a</sup>			
Mean (SD)	39.2 (9.4)	38.3 (10.6)	35.7 (13.1)
Median	42	42	42
Min	1	1	1
Max	64	58	56
Total exposure (patient-years <sup>b</sup> )	33.2	32.8	30.4
Compliance during randomized phase			
≥80% and ≤120%	301 (97.4)	306 (97.1)	303 (97.1)
<80%	4 (1.3)	6 (1.9)	7 (2.2)
>120%	4 (1.3)	3 (1.0)	2 (0.6)

<sup>a</sup> Does not include treatment withdrawal period for Study 6.

<sup>b</sup> Includes treatment withdrawal period for Study 6.

Refer to [Section 1.2 in 2.7.4 Summary of Clinical Safety, Module 2](#).

N Number of patients in dose group. n Number of patients in analysis subgroup. PLA Placebo. QTP XR. Quetiapine XR.  
 Study 6 Study D1448C00006. Study 7 Study D1448C00007.

Note: Patient-years defined as the sum of the duration of exposure across patients in days divided by 365.

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The sponsor did a literature search and post marketing search.

### 7.2.2.1 Other studies

n/a

### 7.2.2.2 Postmarketing experience

There is extensive postmarketing experience. That experience is consistent with this review.

### 7.2.2.3 Literature

There were literature references presented without methodology as to where the literature was obtained. There were no significant findings in the literature presented that are inconsistent with this review or the existing label.

### 7.2.3 Adequacy of Overall Clinical Experience

By agreement the studies provide an adequate clinical experience.

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

N/A

### 7.2.5 Adequacy of Routine Clinical Testing

This testing was adequate.

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

N/A

### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

### 7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of data is adequate.

### 7.2.9 Additional Submissions, Including Safety Update

N/A

## 7.4 General Methodology

The general methodology of these studies are adequate.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The studies in this submission used SEROQUEL XR at doses of 50 mg, 150 mg, and 300 mg once daily. The sponsor recommends dosing as follows in their draft label.

Initial dosing should begin at 50 mg on Days 1 and 2, and be increased to 150 mg on Days 3 and 4. On Day 5 and onwards, if necessary, adjustments can be made upwards or downwards within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient.

For maintenance therapy in major depressive disorder the effective dose during initial treatment should be continued. The dose can be adjusted within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient.

## **8.2 Drug-Drug Interactions**

There was no evidence from the SAE reports that quetiapine XR interacted with other medications during the acute monotherapy, acute adjunct therapy, and maintenance studies. Adjunct therapy with quetiapine XR at doses of 150mg/day or 300mg/day did not appear to have a consistent overall effect on the plasma concentrations of any of the adjunct antidepressants and their metabolites.

## **8.3 Special Populations**

Safety in special groups defined by sex, age and race was explored by tabulating adverse event incidence by those factors. The incidence of common AEs in patients was generally consistent across gender, age from 18 to 65 and race in both monotherapy and adjunct treatment trials, and did not give rise to any new safety issues regarding the use of quetiapine XR in special groups and situations.

## **8.4 Pediatrics**

AstraZeneca is currently working to fulfill the Written Request through the conduct of a pediatric clinical development program. On February 11, 2003, the Division issued a Pediatric Written Request for SEROQUEL Tablets (NDA 20-639) for the treatment of schizophrenia and bipolar mania. The Division agreed (October 11, 2005) that one pharmacokinetic study comparing the XR and immediate-release (IR) formulations of quetiapine will satisfy AstraZeneca's pediatric study obligations for SEROQUEL XR, provided that the IR formulation is demonstrated to be efficacious in pediatric patients in the Pediatric Written Request program.

## **8.5 Advisory Committee Meeting**

I do not feel a meeting is needed.

## 8.6 Literature Review

There were literature references presented without methodology. There were no new significant findings in the literature.

## 8.7 Postmarketing Risk Management Plan

No special plan is required beyond the usual procedures.

## 9 OVERALL ASSESSMENT

I will list selected points derived from the sponsor's analysis that I have verified and am in agreement with.

### Acute monotherapy

A higher incidence of adverse events was seen for quetiapine XR-treated patients compared to placebo-treated patients. This incidence was higher in the quetiapine XR 150 mg/day and 300 mg/day groups than in the 50 mg/day group. The most common adverse events associated with quetiapine XR treatment were dry mouth, sedation, somnolence, and dizziness. The incidence of syncope was low and similar in all treatment groups. The incidence of AEs were similar irrespective of age, race, sex, or region and showed no consistent relationship to dose group.

The initial dose of 50 mg daily and the subsequent titration schedule was safe and well-tolerated for quetiapine-treated patients. The incidence of discontinuations due to adverse events was 5.2% for the placebo group, 8.8% for the quetiapine XR 50 mg/day group, 15.8% for the quetiapine XR 150 mg/day group, and 16.4% for the quetiapine XR 300 mg/day group. The predominant symptoms leading to discontinuation were somnolence and sedation. After titration to the assigned dose, rates of discontinuation were low for all treatment groups.

A higher proportion of reports of extrapyramidal symptoms (EPS) was observed for quetiapine XR-treated patients (5.4%) compared to placebo-treated patients (3.2%). The symptoms were mild to moderate in intensity and seldom led to discontinuation.

The incidence of suicidality was low and similar for both quetiapine XR-treated patients and placebo-treated patients.

No clinically important effects on vital signs were observed for quetiapine XR-treated patients compared to placebo-treated patients.

The incidence of patients showing a weight gain from baseline of  $\geq 7\%$  of body weight was 2.4% in the placebo group, 1.1% in the quetiapine XR 50 mg/day

group, 3.8% in the quetiapine XR 150 mg/day group, and 5.5% in the quetiapine XR 300 mg/day group.

An increase in triglyceride values was observed for quetiapine XR-treated patients compared to placebo-treated patients.

The mean change in glucose appeared to be dose dependent and shifts to clinically important glucose values were greatest in the quetiapine XR 300 mg/day dose group for patients defined as being at risk for diabetes.

Treatment emergent diabetes was not observed for quetiapine XR-treated patients compared to placebo-treated patients.

Abrupt discontinuation of treatment resulted in an increased incidence of mild to moderate adverse events in quetiapine XR-treated patients (23.8%) compared to placebo-treated patients (14.8%). These symptoms usually resolved within one week. The incidence of these discontinuation symptoms were mitigated by gradual down-titration from the 300 mg/day dose.

### **Acute adjunct therapy**

A higher incidence of adverse events was seen for quetiapine XR-treated patients compared to placebo-treated patients. The most common adverse events associated with quetiapine XR treatment were dry mouth, sedation, somnolence, and dizziness. The incidence of syncope was low and similar in all treatment groups. Most adverse events were mild to moderate in intensity. The incidence of AEs were similar irrespective of age, race, sex, or region and showed no consistent relationship to dose group.

The initial dose of 50 mg daily and the subsequent titration schedule was safe and well-tolerated for quetiapine-treated patients. The incidence of discontinuations due to adverse events was 1.9% for the placebo group, 8.9% for the quetiapine XR 150 mg/day group, and 15.4% for the quetiapine XR 300 mg/day group. The predominant symptoms leading to discontinuation were somnolence and sedation. After titration to the assigned dose, rates of discontinuation were low for all treatment groups.

A higher incidence of discontinuation due to adverse events was observed for quetiapine XR-treated patients compared to placebo-treated patients. This rate was higher in the quetiapine XR 300 mg/day group compared to the quetiapine XR 150 mg/day group.

The proportion of reports of extrapyramidal symptoms (EPS) was 4.2% for the placebo group, 3.8% for the quetiapine XR 150 mg/day group, and 6.4% for the quetiapine XR 300 mg/day group. The symptoms were mild to moderate in

intensity and seldom led to discontinuation. Increases in EPS, as determined by changes in SAS and BARS scores, were similar in all treatment groups.

The incidence of suicidality was low and similar for both quetiapine XR-treated patients and placebo-treated patients.

No clinically important effects on vital signs were observed for quetiapine XR treated patients compared to placebo-treated patients.

The incidence of patients showing a weight gain from baseline of  $\geq 7\%$  of body weight was 1.7% in the placebo group, 3.2% in the quetiapine XR 150 mg/day group, and 7.2% in the quetiapine XR 300 mg/day group.

An increase in triglyceride and cholesterol values was observed for quetiapine XR treated patients compared to placebo-treated patients.

The effects of quetiapine XR treatment on glucose regulation parameters appeared to be small in comparison to that of placebo. The mean change in glucose was greater in the quetiapine XR 300 mg/day group than in the quetiapine XR 150 mg/day group. Shifts to clinically important glucose values were greatest in the quetiapine XR 300 mg/day dose group and for patients defined as being at risk for diabetes.

Treatment emergent diabetes was not observed for quetiapine XR-treated patients compared to placebo-treated patients.

Abrupt discontinuation of treatment resulted in an increased incidence of mild to moderate adverse events in quetiapine XR-treated patients compared to placebo treated patients. These symptoms usually resolved within one week.

### **Maintenance therapy**

The proportion of reports of extrapyramidal symptoms (EPS) during prolonged exposure (randomization phase) was 1.8% for the placebo group and 2.8% for the quetiapine XR group. The symptoms were mild to moderate in intensity and seldom led to discontinuation. Increases in EPS, as determined by changes in SAS and BARS scores, were similar in all treatment groups.

The incidence of patients showing a weight gain of  $\geq 7\%$  of body weight during prolonged exposure (randomization phase) was 2.9% in the placebo group and 5.4% in the quetiapine XR group.

During prolonged exposure (randomization phase) triglyceride values decreased in both the quetiapine XR and placebo treatment groups.

## **9.1 Conclusions**

The safety data in this submission are generally consistent with current labeling for Seroquel SR. No new safety issues have been identified.

## **9.2 Recommendation on Regulatory Action**

I recommend the three supplements for MDD be approved.

## **9.3 Recommendation on Postmarketing Actions**

### 9.3.1 Risk Management Activity

There are no recommendations other than the usual procedures.

### 9.3.2 Required Phase 4 Commitments

None.

### 9.3.3 Other Phase 4 Requests

None

## **9.4 Labeling Review**

The labeling must be reworded so that no claims are made regarding HAM-A claims.

Also the claim that a significant improvement was observed within the first week is not justified.

The sexual claims should not be celebrated in the label.

## **9.5 Comments to Applicant**

Labeling changes will need to be communicated.

## 10 APPENDICES

### 10.1 Line-by-Line Labeling Review

The labeling was updated for the increased exposure in many safety sections. Labeling was added for the new indications. The key sections are presented below. I have indicated suggested changes elsewhere in this review.

AstraZeneca is proposing a table for dosing in the highlights section. Currently, all proposed indications have been included and, if accepted, will be modified as indications are approved.

#### 1.1 Major Depressive Disorder

SEROQUEL XR is indicated for the treatment of major depressive disorder as:

- monotherapy or adjunct therapy to other antidepressants
- maintenance of antidepressant effect

The efficacy of SEROQUEL XR was demonstrated in 6 clinical trials in patients with major depressive disorder. Of these trials, 3 were monotherapy, 2 were adjunct therapy to other antidepressants and 1 was maintenance of antidepressant effect. [see Clinical Studies (14.1)].

#### 2.1 Major Depressive Disorder

Antidepressant efficacy was demonstrated with SEROQUEL XR at doses of 50 mg, 150 mg, and 300 mg once daily.

Initial dosing should begin at 50 mg on Days 1 and 2, and be increased to 150 mg on Days 3 and 4. On Day 5 and onwards, if necessary, adjustments can be made upwards or downwards within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient.

For maintenance therapy in major depressive disorder the effective dose during initial treatment should be continued. The dose can be adjusted within the dose range of 50 mg to 300 mg depending upon the clinical response and tolerance of the patient. [see Clinical Studies (14.1)].

## 2.4 Maintenance Treatment

While there is no body of evidence available to specifically address how long the patient treated with SEROQUEL XR should remain on it, a longer-term schizophrenia study with SEROQUEL XR has shown this drug to be effective in delaying time to relapse in patients who were stabilized on SEROQUEL XR at doses of 400 to 800 mg/day for 16 weeks [see *Clinical Studies* (14.2)]. In addition, a longer-term major depressive disorder study with SEROQUEL XR has shown this drug to be effective in maintaining antidepressant effect in patients who were stabilized on SEROQUEL XR at doses of 50 to 300 mg/day for 12 weeks [see *Clinical Studies* (14.1)]. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment. [see *Clinical Studies* (14.2)].

## 3 DOSAGE FORMS AND STRENGTHS

50 mg extended-release tablets

200 mg extended-release tablets

300 mg extended-release tablets

400 mg extended-release tablets

### 5.18 Suicide

In six, 6- and 8-week clinical studies in patients with major depressive disorder (n=2733, 1776 on SEROQUEL XR and 957 on placebo) the incidence of treatment emergent suicidal ideation or suicide attempt was 0.7% in SEROQUEL XR treated patients and 0.7% in placebo. In a longer-term 52-week study in patients with major depressive disorder (n=776, 391 for SEROQUEL XR and 385 for placebo) the incidence was 0.3% for SEROQUEL XR and 0.5% for placebo.

### 6.0

#### Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

There was no difference in the incidence and type of adverse reactions associated with discontinuation (6.4% for SEROQUEL XR vs. 7.5% for placebo) in a pool of schizophrenia controlled trials. In monotherapy clinical trials in patients with major depressive disorder 14.3% of patients on SEROQUEL XR discontinued due to adverse reaction compared to 5.2% on placebo. In adjunct therapy clinical trials in patients with major depressive disorder 8.9% of patients on SEROQUEL XR discontinued due to adverse reaction compared to 1.9% on placebo.

<sup>25</sup>Summary of Clinical Safety  
2.7.4.1.2.2.1 and 2.7.4.1.2.2.2

<sup>7</sup>Summary of Clinical Efficacy  
2.7.3.3.2.3.1

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during short-term monotherapy of major depressive disorder (up to 8 weeks) in ≥ 5% patients treated with SEROQUEL XR (doses 50mg, 150mg and 300 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

<sup>27</sup>Summary of Clinical Safety  
 2.7.4.2.1.2.2, and SA043d

**Table 3. Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Monotherapy Clinical Trials for the Treatment of Major Depressive Disorder<sup>1</sup>**

<u>Body System/Preferred Term</u>	<u>SEROQUEL XR (n=1149)</u>	<u>PLACEBO (n=648)</u>
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**Gastrointestinal Disorders**

<u>Dry mouth</u>	<u>35%</u>	<u>8%</u>
<u>Constipation</u>	<u>8%</u>	<u>4%</u>

**General Disorders and Administration Site**

**Conditions**

<u>Fatigue</u>	<u>7%</u>	<u>3%</u>
<u>Irritability</u>	<u>5%</u>	<u>4%</u>

**Metabolism and Nutrition Disorders**

<u>Increased Appetite</u>	<u>5%</u>	<u>3%</u>
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**Nervous System Disorders**

<u>Sedation</u>	<u>29%</u>	<u>5%</u>
<u>Somnolence</u>	<u>25%</u>	<u>7%</u>
<u>Dizziness</u>	<u>15%</u>	<u>9%</u>

<sup>1</sup>Reactions for which the SEROQUEL XR incidence was ≥5% but equal to or less than placebo are not listed in the table, but included the following: diarrhea, headache, insomnia, and nausea.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were dry mouth (35%), sedation (29%), somnolence (25%), constipation (8%), and fatigue (7%).

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during short-term adjunct therapy of major depressive disorder (up to 6 weeks) in ≥ 5% patients treated with SEROQUEL XR (doses 150 mg and 300 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

**Table 4. Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Adjunct Therapy Clinical Trials for the Treatment of Major Depressive Disorder<sup>1</sup>**

<u>Body System/Preferred</u>	<u>SEROQUEL XR (n=627)</u>	<u>PLACEBO (n=309)</u>
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**Term**

**Gastrointestinal Disorders**

<u>Dry Mouth</u>	<u>33%</u>	<u>8%</u>
<u>Constipation</u>	<u>8%</u>	<u>4%</u>

**General Disorders and Administration Site**

**Conditions**

	<u>13%</u>	<u>4%</u>
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**Fatigue**

**Nervous System Disorders**

<u>Somnolence</u>	<u>24%</u>	<u>4%</u>
<u>Sedation</u>	<u>15%</u>	<u>4%</u>
<u>Dizziness</u>	<u>11%</u>	<u>7%</u>

<sup>1</sup>Reactions for which the SEROQUEL XR incidence was >5% but equal to or less than placebo are not listed in the table, but included the following: headache, insomnia and nausea.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were dry mouth (33%), somnolence (24%), sedation 15%, fatigue (13%), and constipation (8%).

In a longer-term placebo-controlled trial, adult patients with major depressive disorder who remained clinically stable on SEROQUEL XR during open label treatment for at least 12 weeks were randomized to placebo (n=385) or to continue on SEROQUEL XR (n=391) for up to 52 weeks of observation for possible relapse. Table 5 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during longer-term treatment of major depressive disorder in ≥ 5% patients treated with SEROQUEL XR (doses 50 mg and 300 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

**Table 5. Treatment-Emergent Adverse Reaction Incidence in a Longer-Term Clinical Trial for the Treatment of Major Depressive Disorder<sup>1</sup>**

	<u>SEROQUEL XR (n=391)</u>	<u>Placebo (n=385)</u>
<u>Weight Gain</u>	<u>10%</u>	<u>2%</u>
<u>Dizziness</u>	<u>7%</u>	<u>4%</u>
<u>Arthralgia</u>	<u>5%</u>	<u>2%</u>

<sup>1</sup>Reactions for which the SEROQUEL XR incidence was >5% but equal to or less than placebo are not listed in the table, but included the following: headache, nasopharyngitis, insomnia and diarrhea.

In four short-term placebo-controlled monotherapy clinical trials for the treatment of major depressive disorder utilizing between 50 mg and 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 5.4% for SEROQUEL XR and 3.2% in the placebo group. In two placebo-controlled short-term adjunct therapy clinical trials for the treatment of major depressive disorder utilizing between 150 mg and 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 5.1% SEROQUEL XR and 4.2% for the placebo group. In one longer-term placebo-controlled clinical trial for the treatment of major depressive disorder utilizing between 50 mg and 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 2.8% for SEROQUEL XR and 1.8% in the placebo group.

### Sexual Dysfunction

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacological treatment.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

Table 6 shows the incidence rates of sexual adverse Effects in patients with major depressive disorder in placebo controlled-trials. In SEROQUEL XR and placebo treated patients, the total incidence of adverse effects related to sexual dysfunction was generally low ( $\leq 1.5\%$ ) and did not exceed 0.6% in any individual item.

<sup>33</sup>Summary of Clinical  
Safety 2.7.4.2.1.6.6,  
2.7.4.4.2.6.1 and  
2.7.4.4.2.6.2

**Table 6: Incidence of Sexual Adverse Effects in Placebo-Controlled Major Depressive Disorder Clinical Trials**

<b><u>Short-term Monotherapy Trials</u></b>		
	<u>SEROQUEL XR</u> (n=1149)	<u>Placebo</u> (n=648)
<u>Total</u>	<u>1.4%</u>	<u>1.2%</u>
<u>Anorgasmia</u>	<u>0.3%</u>	<u>0%</u>
<u>Dyspareunia</u>	<u>0.1%</u>	<u>0%</u>
<u>*Ejaculation delayed</u>	<u>0.1%</u>	<u>0%</u>
<u>*Erectile dysfunction</u>	<u>0.3%</u>	<u>0.5%</u>
<u>Libido decreased</u>	<u>0.5%</u>	<u>0.5%</u>
<u>Loss of Libido</u>	<u>0%</u>	<u>0.2%</u>
<u>Orgasm abnormal</u>	<u>0.1%</u>	<u>0%</u>
<u>Vulvovaginal dryness</u>	<u>0.1%</u>	<u>0.2%</u>

<b><u>Short-Term Adjunct Therapy Trials</u></b>		
	<u>SEROQUEL XR</u> (n=627)	<u>Placebo</u> (n=309)
<u>Total</u>	<u>0.9%</u>	<u>0.3%</u>
<u>Libido decreased</u>	<u>0.6%</u>	<u>0%</u>
<u>Libido increased</u>	<u>0 %</u>	<u>0.3%</u>
<u>Loss of Libido</u>	<u>0.1%</u>	<u>0%</u>
<u>Sexual dysfunction</u>	<u>0.1%</u>	<u>0%</u>

\*occurred only in males

In one longer-term maintenance study, the incidence of adverse effects potentially associated with sexual dysfunction was 1.5% for SEROQUEL XR and 0.5% for placebo.

There are no adequately designed studies examining sexual dysfunction with quetiapine treatment. While it is difficult to know the precise risk of sexual dysfunction associated with the use of quetiapine, physicians should routinely inquire about such possible side effects.

Antidepressants:  
Coadministration of amitriptyline, bupropion,  
citalopram, duloxetine, escitalopram, fluoxetine, paroxetine,  
sertraline and venlafaxine with quetiapine did not appear to  
have a consistent overall effect on the plasma concentrations of  
the coadministered drug.

<sup>37</sup>Summary of Clinical  
Pharmacology Studies,  
2.7.2.3.1.2

<sup>42</sup>Summary of Clinical Efficacy  
2.7.3.3.1.1.1 and 2.7.3.3.2.1.1

## 14 CLINICAL STUDIES

### 14.1 Major Depressive Disorder

The efficacy of SEROQUEL XR in the treatment of major depressive disorder (MDD) was established in 3 placebo-controlled monotherapy clinical trials, 2 adjunct therapy clinical trials, and 1 monotherapy, placebo-controlled maintenance trial. All trials included patients who met DSM-IV criteria for major depressive disorder, single or recurrent episodes, with and without psychotic features.

<sup>43</sup>Summary of Clinical Efficacy  
2.7.3.3.1.4.1 Tables E24 and E 25

#### Monotherapy

The efficacy of SEROQUEL XR as monotherapy in the treatment of MDD was demonstrated in two 6-week placebo-controlled, fixed dose trials, and one 8-week placebo-controlled, modified fixed dose trial (optional one time dose increase) (n=1445). The primary endpoint in these trials was the change from baseline to week 6 or 8 in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10 item clinician-rated scale used to assess the degree of depressive symptomatology (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts) with total scores ranging from 0 (no depressive features) to 60 (maximum score). A Hamilton Rating Scale for Depression (HAM-D-17) total score of >22 was a requirement for study entry; the mean HAM-D total score at entry was 26, and 23% percent of patients scored 28 or greater.

<sup>44</sup>Summary of Clinical Efficacy  
2.7.3.3.2.1.1 and 2.7.3.3.2.1.3

<sup>45</sup>Summary of Clinical Efficacy  
2.7.3.3.2.1.8

<sup>46</sup>Summary of Clinical Efficacy  
2.7.3.3.1.1.2 and 2.7.3.3.2.2.1

SEROQUEL XR at a dose of 50 mg, 150 mg, and 300 mg once daily was superior to placebo in reduction of depressive symptoms as measured by change in MADRS total score, with significant improvement observed within the first week (Days 4 and 8) and continuing throughout the study. Superior improvements were also seen in anxiety symptoms as measured by the Hamilton Rating Scale for Anxiety (HAM-A).

#### Adjunct Therapy

The efficacy of SEROQUEL XR as adjunct therapy in the treatment of MDD was demonstrated in two 6-week placebo-controlled, fixed dose trials (n=936). The primary endpoint for these trials was the change from baseline to end of treatment (week 6) in the MADRS total score. A HAM-D-17 total score of >20 was a requirement for study entry; the mean HAM-D total score at entry was 24, and 17 percent of patients scored 28 or greater. SEROQUEL XR at a dose of 150 mg/day or 300 mg/day once daily was given as adjunct to existing antidepressant therapy in patients who had previously shown an inadequate response to at least one antidepressant.

<sup>48</sup>Clinical Study Report D1448C00006 section 5.1 and D1448C00007 section 5.1

Inadequate response was defined as having continued depressive symptoms for the current episode (HAM-D total score of >20) despite using an antidepressant for 6 weeks at or above the minimally effective labeled dose. Patients were on various antidepressants prior to study entry including SSRI's (paroxetine, fluoxetine, sertraline escitalopram, or citalopram), SNRI's, (duloxetine and venlafaxine,) TCA (amitriptyline) and other (bupropion).

<sup>49</sup>Summary of Clinical Efficacy 2.7.3.3.2.2.1 and  
<sup>50</sup>Summary of Clinical Efficacy 2.7.3.3.2.2.8

SEROQUEL XR 300 mg once daily as adjunct treatment to other antidepressant therapy was superior to antidepressant alone in reduction of MADRS total score in both trials, with improvement in depressive symptoms seen at week 1 through end of study (6 weeks). SEROQUEL XR 150 mg once daily as adjunct treatment was superior to antidepressant therapy alone in reduction of MADRS total score in one trial, with improvement in depressive symptoms seen at week 1 through end of study (6 weeks). Superior improvements in anxiety symptoms as measured by the HAM-A were also seen.

<sup>51</sup>Summary of Clinical Efficacy 2.7.3.3.1.1.3  
<sup>52</sup>Clinical Study Report D1448C00005 section 5.1

### Maintenance

A longer-term, maintenance clinical trial consisted of open-label run-in treatment and stabilization phases followed by a double-blind randomized treatment phase. 1854 patients entered the open-label phase and received SEROQUEL XR. Patients who had a HAM D-17 score of 20 or greater received SEROQUEL XR (flexibly dosed at 50 mg, 150 mg, or 300 mg once daily) for 4 to 8 weeks. Patients who were stabilized (CGI-S  $\leq$ 3 and a MADRS total score  $\leq$ 12) received SEROQUEL XR for an additional 12 to 18 weeks, within the same dose range. Stability was defined as above with the additional requirement of MADRS total score not to exceed 15 for two consecutive visits and CGI-S not to exceed 5 at any visit.

<sup>53</sup>Summary of Clinical Efficacy 2.7.3.3.1.1.3

<sup>47</sup>Summary of Clinical Efficacy 2.7.3.3.1.4.2 Tables E26

Patients meeting these criteria (n=771) were randomized to placebo or to continue on SEROQUEL XR for up to 52 weeks. Relapse during the double-blind phase was defined as: initiation of other drug treatment by the investigator; additional antidepressant treatment by

the patient for at least 1 week; hospitalization; MADRS total score  $\geq 18$  at 2 consecutive assessments one week apart or the final assessment if patient discontinues; CGI-S score  $\geq 5$ ; or suicide attempt or imminent risk of suicide.

<sup>54</sup>Summary of Clinical Efficacy 2.7.3.3.2.3.1

Patients on SEROQUEL XR (mean dose 177 mg/day) experienced a statistically significant longer time to relapse than did patients on placebo.

## **REFERENCES**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

**CHEMISTRY REVIEW(S)**

**Division of Post Approval Marketing Evaluation IV  
Chemist Review of Supplement**

1. Division of Post Approval Marketing IV
2. NDA Number: 22047
3. Supplement Numbers/Dates: SE1- 010, 011, 012  
Letter Date: February 27, 2008  
Stamp Date: February 27, 2008
4. Amendments/Reports/Dates:
5. Received by Chemist: May 19, 2008
  
6. Applicant Name and Address: Astra Zeneca  
1800 Concord Pike  
PO BOX 8355  
Wilmington DE 19803-8355
  
7. Name of the Drug: Seroquel XR Tablets
8. Nonproprietary name: quetiapine fumarate
9. Chemical Structure/ Chemical Name:
- 10: Dosage Form: Tablets
11. Potency: 50, 200, 300 and 400mg
12. Pharmacological Category: Depression
13. How Dispensed: XXX (RX) \_\_\_\_\_ (OTC)
14. Records and Reports current XXX (yes) \_\_\_\_\_ (No)
15. Related IND/NDA/DMF: \_\_\_\_\_ (yes) XXX (No)

(b) (4)

**16. Comments and Conclusions :** These bundled PA Supplements provide for a new indication for treatment of monotherapy, adjunct therapy and maintenance therapy in the treatment of major depressive disorder. No new CMC information is provided in these submissions. An environmental assessment has been prepared by the Sponsor. An EIC of  ppb is based on all AZ's drug products containing quetiapine based on the largest projected production forecast for direct use, per year for the years of 2007 to 2012. The use is predicted to result from metabolites rather than active moiety. Since the new indication does not increase the active moiety, a request has been made for categorical exclusion under 21 CFR 25.31 (a). The environmental assessments, as submitted by the Sponsor, have been reviewed by Raanan Bloom wherein the claim for categorical exclusion is concurred. (Email to T. Bouie from R. Bloom, May 20, 2008).

**17. Conclusions:** *This submission is for a new indication for the Seroquel® drug product. There are no changes to the CMC for the drug substance or product.*

**Recommendations:** Recommend Approval of this Supplement.

19. Reviewer Name

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 Julia C. Pinto, Ph.D., Chemist

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**NDA/Serial Number:** 22-047 / S-010, S-011, S-012

**Drug Name:** Seroquel XR (quetiapine fumarate)

**Indication(s):** Major Depressive Disorder (monotherapy, adjunctive therapy, and maintenance)

**Applicant:** AstraZeneca

**Date(s):** Received: Feb 27, 2008;  
PDUFA Due Date: Dec 27, 2008

**Review Priority:** Standard

**Biometrics Division:** Biometrics I, HFD-710

**Statistical Reviewers:** Phillip Dinh, Ph.D.

**Concurring Reviewers:** Peiling Yang, Ph.D.  
H.M. James Hung, Ph.D.

**Medical Division:** Division of Psychiatric Products, HFD-130

**Clinical Team:** Earl Hearst M.D., Medical Reviewer, HFD-130  
Robert Levin M.D., Medical Team Leader, HFD-130

**Project Manager:** Renmeet Grewal, Pharm.D., HFD-130

**Keywords:** Clinical studies; NDA review

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

The sponsor submitted seven efficacy and safety studies to seek claims for monotherapy, adjunctive therapy, and maintenance treatment for adult patients with major depressive disorder (MDD). Evidence of effectiveness for the monotherapy was demonstrated from three studies: D1448C00001, D1448C00002, and D1448C00003. Evidence of effectiveness for the adjunctive therapy to an antidepressant was demonstrated from two studies: D1448C00006 and D1448C00007. Evidence of effectiveness for maintenance therapy was demonstrated from one study: D1448C00005.

In studies D1448C00001, D1448C00002, D1448C00003, D1448C00006, and D1448C00007, the primary efficacy variable was the change from randomization to end visit (week 6 or week 8) in the Montgomery-Asberg Depression Rating (MADRS) total score. The Hamilton Rating Scale for Anxiety (HAM-A) was not a pre-specified endpoint, thus it can only serve as exploratory findings and do not support labeling claims. Furthermore, the claim that significant improvement was observed within the first week and continuing through the study was not justified because there were not appropriate statistical methods pre-specified.

### 1.2 Brief Overview of Clinical Studies

Study D1448C00001 was an 8-week, United States, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The double-blind treatment phase lasted for 6 weeks. Three doses of quetiapine XR were investigated: 50 mg/day, 150 mg/day, and 300 mg/day. The randomized sample consisted of 725 subjects between the age of 18 and 65 years. The primary efficacy variable was the change from randomization to week 6 in the MADRS total score. The key secondary variable was the change from randomization to week 6 in the Quality of Life Enjoyment Satisfaction Questionnaire (Q-LES-Q) percent maximum total score.

Study D1448C00002 was an 8-week, United States, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The double-blind treatment phase lasted 6 weeks. Quetiapine XR at 150 mg/day and 300 mg/day were investigated. The study also included duloxetine 60 mg/day as assay sensitivity. The randomized sample consisted of 612 patients between the age of 18 and 65 years. The primary efficacy variable was the change from randomization to week 6 in the MADRS total score. The key secondary variable was the change from randomization to week 6 in the Q-LES-Q percent maximum total score.

Study D1448C00003 was a 10-week, United States, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized, modified fixed-dosed study. The randomized double-blind treatment period lasted 8 weeks. Patients were randomized to either quetiapine XR 150 mg/day or placebo. After 2 weeks of treatment, patients with an inadequate response were up-titrated to 300 mg/day or matching placebo. Three hundreds and ten subjects between the age of 18 and 65 years were randomized. The primary

efficacy variable was the change from randomization to week 8 in the MADRS total score. The key secondary variable was the change from randomization to week 8 in the Q-LES-Q percent maximum total score.

Study D1448C00005 was an international, multi-center, randomized-withdrawal, parallel-group, double-blind, placebo-controlled study. The study consisted of 4 periods: an enrollment period of up to 28 days, an open-label run-in treatment period of 4 to 8 weeks, the open-label stabilization treatment period of 12 to 18 weeks, and a double-blind, randomized treatment period of up to 52 weeks. In this study, quetiapine XR could be adjusted to 50, 150, or 300 mg/day to maximize efficacy and tolerability. The randomized sample consisted of 776 patients between the age of 18 and 65 years. The primary efficacy variable was the time from randomization to a depressed event.

Study D1448C00006 was an 8-week, United States, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized, adjunctive therapy study. The double-blind treatment period lasted 6 weeks. Two doses of quetiapine XR were under investigation: quetiapine XR 150 mg/day and quetiapine XR 300 mg/day (in combination with an antidepressant). The randomized sample consisted of 446 patients between the age of 18 and 65 years who had inadequate responses to an antidepressant. The primary efficacy variable was the change from randomization to week 6 in the MADRS total score. The key secondary variable was the change from randomization to week 6 in the Q-LES-Q percent maximum total score.

Study D1448C00007 was a 6-week, international, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized, adjunctive therapy study. The double-blind treatment period lasted 6 weeks. Two doses of quetiapine XR were under investigation: quetiapine XR 150 mg/day and quetiapine XR 300 mg/day (in combination with an antidepressant). The randomized sample consisted of 493 patients between the age of 18 and 65 years who had inadequate responses to an antidepressant. The primary efficacy variable was the change from randomization to week 6 in the MADRS total score. The key secondary variable was the change from randomization to week 6 in the Q-LES-Q percent maximum total score.

In addition to these six studies, the sponsor also submitted study D1448C00004. Study D1448C00004 was an international, multi-center, double-blind, randomized, parallel-group, placebo-controlled, modified fixed-dosed study. The study investigated quetiapine XR 150/300 mg against placebo. The study also included escitalopram for assay sensitivity. This study was considered a failed study because both quetiapine XR and escitalopram did not separate from placebo. This study is not included in this review.

### **1.3 Statistical Issues and Findings**

All six studies were positive on the primary efficacy variable on at least one dose under investigation. Among five studies that had the key secondary endpoint (Q-LES-Q percent maximum score), none of the studies was positive on the key secondary endpoint. The HAM-A was not a pre-specified endpoint, thus it cannot be used to support labeling claims.

Although the numerical evidence suggested that patients who took quetiapine XR benefited from the treatment early in the course of the trials, no appropriate statistical methods were pre-specified to assess this claim formally. Thus the claim that a significant improvement was observed within the first week and continuing throughout the study was not justified and could only be used descriptively.

## **2. INTRODUCTION**

### **2.1 Overview**

This review provides a statistical evaluation of quetiapine XR as a monotherapy, adjunctive therapy, and maintenance therapy for major depressive disorder (MDD).

According to the sponsor, quetiapine is a dibenzothiazepine derivative. The immediate-release (IR) formulation was approved by the Food and Drug Administration (FDA) in September 1997 for the treatment of schizophrenia, in January 2004 for the treatment of bipolar mania, and in October 2006 for the treatment of depressive episodes associated with bipolar disorder. Quetiapine XR is an extended-release formulation of quetiapine. The formulation was approved in May 2007 for the treatment of schizophrenia.

MDD is a psychiatric disorder characterized by the presence of one or more depressive episodes without a history of manic, mixed, or hypo-manic episodes. The lifetime prevalence of MDD varies from 6.7% to as much as 13.2%. MDD affects about 120 million people worldwide and is among the leading causes of disability. The burden of the illness is high on the patients and on the society. It is estimated that up to 15% of patients with severe major depressive episodes commit suicide. Patients with MDD often have decreased social, occupational, and educational functioning. There are currently more than 25 agents approved for the treatment of MDD; however, it is estimated that 10% to 20% of depressed patients are unable to tolerate the treatment. Furthermore, 25% to 35% of those who complete a generally prescribed course of an approved antidepressant do not show an acceptable response.

In an attempt to expand the treatment options to MDD patients, AstraZeneca has been investigating the efficacy and safety of quetiapine XR in an extensive clinical program. The program included 7 phase III, safety and efficacy studies: four studies where quetiapine XR was investigated as a monotherapy (studies D1448C00001, D1448C00002, D1448C00003, D1448C00004), two studies where quetiapine XR was investigated as an adjunctive therapy to an antidepressant (studies D1448C00006, D1448C00007), and one study as a maintenance therapy (study D1448C00005).

In study D1448C00004, both quetiapine XR and the active control (escitalopram) did not separate from placebo. This study will be not evaluated in this review.

### **2.2 Data Sources**

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room:

\\Cdsesub1\evsprod\NDA022047\0007.

### 3. STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

##### 3.1.1 Study D1448C00001

###### 3.1.1.1 Objectives

Primary: The primary objective of this study was to evaluate the efficacy of 3 doses of quetiapine XR versus placebo in the change from randomization to Week 6 in the Montgomery-Asberg Depression Rating (MADRS) total score.

Key Secondary: The key secondary objective was to evaluate if quetiapine XR improved the health-related quality of life in patients with major depressive disorder (MDD) by evaluating the change from randomization to Week 6 in Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) total score.

###### 3.1.1.2 Study Design

This was an 8-week, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The study enrolled subjects from 38 centers in the United States. The study consisted of three periods. The washout period lasted from 7 days up to 28 days. The double-blind period lasted for six-week in which eligible patients were randomly assigned to 1 of 4 treatment groups: quetiapine XR 50 mg/day, quetiapine XR 150mg/day, quetiapine XR 300 mg/day, or placebo. Patients in the quetiapine XR 150mg/day and quetiapine XR 300 mg/day were titrated to their assigned doses. Following the double-blind period was a two-week post-treatment period where discontinuation symptoms were assessed.

Male and female patients between the age of 18 and 65 years old were enrolled from April 2006 to May 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D (17-item) total score of at least 22 and HAM-D Item 1 (depressed mood) score of at least 2 both at enrollment and at randomization. Assessments of the primary endpoint, MADRS, were done on Days 1, 4, 8, 15, 29, and 43. Assessments of the key secondary endpoint, Q-LES-Q, were done on Days 1, 29, and 43.

It was determined that 166 patients/arm were needed to detect a 3.5 unit difference (standard deviation of 9) for the change in the MADRS total score from baseline to Week 6 at a 0.05 level of significance and an 80% power.

###### 3.1.1.3 Efficacy Endpoints and Analyses

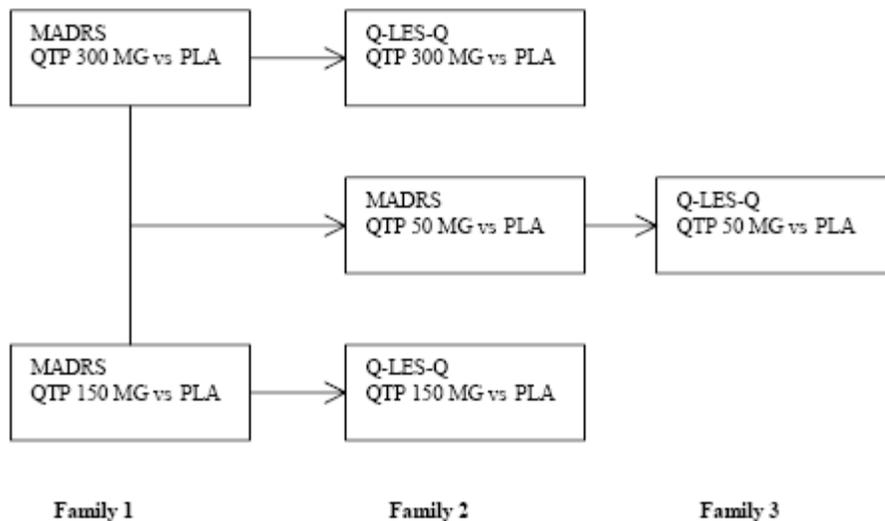
Primary endpoint and analysis: The primary endpoint was the change from randomization to Week 6 in the MADRS total score. Missing values were imputed by the Last Observation Carried Forward (LOCF) method. The primary efficacy variable was analyzed by a mixed model ANCOVA with MADRS total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

Key Secondary endpoint and analysis: The key secondary endpoint was the change in the Q-LES-Q percent maximum total score from randomization to Week 6. The short form of the Q-LES-Q consists of 16 items rated on a 5-point scale. Larger values indicate a higher perceived quality of life enjoyment and satisfaction. The Q-LES-Q total score is the sum of the first 14 items. This total score is converted to a percentage of the maximum score using the scoring conversion:

$$\text{Q-LES-Q percent maximum score} = \frac{\text{Q-LES-Q totals core} - 14}{56} \times 100.$$

Missing values were imputed by the LOCF method. The key secondary endpoint was analyzed by a mixed model with Q-LES-Q percent maximum total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

To control for multiple testing, a tree-structured gatekeeping procedure was employed. The hypotheses tree is presented in Figure 1. In a tree-structured gatekeeping procedure, hypotheses are tested in a hierarchical way. A hypothesis is not tested unless its parental hypotheses are rejected. For example, a 300 mg dose on the Q-LES-Q is not tested unless a 300 mg dose on the MADRS is significant. Likewise, a 50 mg dose on the MADRS is not tested unless either a 300 mg dose or a 150 mg dose is significant on the MADRS. Uniform weights were assumed for all hypotheses in each family.



**Figure 1. Study D1448C00001: Tree gatekeeping structure**  
 (Source: d1448c0001-SAP; Figure 1, page 34)

### 3.1.1.4 Efficacy Results

#### 3.1.1.4.1 Study Population

Subjects were enrolled from 40 centers in the United States. A total of 1075 subjects were screened and 725 subjects were randomized to 1 of the four treatment groups: placebo, quetiapine XR 50 mg, quetiapine XR 150 mg, and quetiapine XR 300 mg. The disposition of the subjects is summarized in Table 1. Approximately 71% of the subjects completed the 6-week randomized treatment period. Among the reasons for discontinuations, adverse events, lost to follow-up, and patients not willing to continue were main reasons. There were more adverse events in the quetiapine XR arms than in the placebo. There were slightly more dropouts in the middle and high dose of quetiapine XR than in the placebo and the low dose.

**Table 1. Study D1448C00001: Disposition of patients**

	Placebo (N = 184)	QTP 50mg (N = 182)	QTP 150mg (N = 178)	QTP 300mg (N = 179)	Total (N = 723)
Randomized (not treated)	3	1	2	0	6
Randomized (treated)	181	181	176	179	717
<b>Discontinued study</b>	<b>50 (27.2)</b>	<b>48 (26.4)</b>	<b>55 (30.9)</b>	<b>59 (33.0)</b>	<b>212 (29.3)</b>
Lost to follow-up	18 (9.8)	14 (7.7)	10 (5.6)	12 (6.7)	54 (7.5)
Adverse event	11 (6.0)	15 (8.2)	25 (14.0)	34 (19.0)	85 (11.8)
Development of study specific discontinuation criteria	1 (0.5)	3 (1.6)		1 (0.6)	5 (0.7)
Patients not willing to continue	10 (5.4)	9 (4.9)	9 (5.1)	8 (4.5)	36 (5.0)
Condition under investigation worsened			1 (0.6)		5 (0.7)
Severe non-compliance to study protocol	2 (1.1)	6 (3.3)	8 (4.5)	3 (1.7)	19 (2.6)
Eligibility criteria not fulfilled	1 (0.5)		2 (1.1)		3 (0.4)
Other	3 (1.6)	1 (0.5)		1 (0.6)	5 (0.7)
<b>Completed 6-week   randomized treatment period</b>	<b>134 (72.8)</b>	<b>134 (73.6)</b>	<b>123 (69.1)</b>	<b>120 (67.0)</b>	<b>511 (70.7)</b>

(Source: d1448c00001 Study Report; Figure 3, pages 80-81)

The demographics and baseline disease characteristics of the modified intent-to-treat (MITT) sample are presented in Table 2. Patients in this study were between 18 and 65 years of age. The average age was 41 years old. There were more females than males. The majority of the subjects was Caucasian (73%) and black (23%). The distribution of the baseline MADRS total score appeared balanced across the four treatment arms.

**Table 2. Study D1448C00001: Demographic and baseline disease characteristics (MITT sample)**

	Placebo N = 178	QTP 50 mg N = 178	QTP 150 mg N = 168	QTP 300 mg N = 176	Total N = 700
<i>Age (yr) n</i>					
Mean (SD)	40.3 (11.8)	40.6 (11.1)	41.5 (11.7)	40.7 (12.2)	40.7 (11.7)
Median	40.5	42.0	43.0	41.0	42.0
Min – Max	18 – 65	18 – 63	19 – 65	18 – 64	18 – 65
<i>Sex – n (%)</i>					
Male	65 (36.5)	83 (46.6)	64 (38.1)	73 (41.5)	285 (40.7)
Female	113 (63.5)	95 (53.4)	104 (61.9)	103 (58.5)	415 (59.3)
<i>Race – n (%)</i>					
Black	35 (19.7)	39 (21.9)	40 (23.8)	44 (25.0)	158 (22.6)
Caucasian	136 (76.4)	131 (73.6)	124 (73.8)	123 (69.9)	514 (73.4)
Oriental	2 (1.1)	2 (1.1)	1 (0.6)	0 (0.0)	5 (0.7)
Others	5 (2.8)	6 (3.4)	3 (1.8)	9 (5.1)	23 (3.3)
<i>Baseline MADRS- total score</i>					
Mean (SD)	30.5 (5.2)	30.9 (4.5)	30.9 (5.0)	30.6 (4.8)	30.7 (4.9)
Median	31.0	31.0	31.0	30.0	31.0
Min – Max	19 – 46	19 – 45	17 – 47	18 – 42	17 – 47

(Source: d1448c00001 Study Report; Tables 14-15, pages 84-85)

#### 3.1.1.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from randomization to Week 6 in the MADRS total score. The primary analysis model was a mixed effect ANCOVA model with baseline MADRS total score as a covariate, treatment as a fixed factor, and center as a random effect. Multiple hypotheses were tested using the tree-structured gatekeeping procedure described above. The primary analysis is summarized in Table 3. All three doses of quetiapine XR were statistically significantly different from placebo.

**Table 3. Study D1448C00001: Sponsor's primary efficacy results: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 50mg	QTP 150mg	QTP 300mg
Sample size	178	178	168	176
LS Means	-11.07	-13.56	-14.50	-14.18
Difference from placebo (95% confidence interval)		-2.50 (-4.48, -0.51)	-3.44 (-5.45, -1.42)	-3.11 (-5.10, -1.12)
Unadjusted p-values		0.014	0.001	0.002
Adjusted p-values		0.042	0.002	0.004

(Source: d1448c00001 Study Report; Table 17, pages 90-91)

#### 3.1.1.4.3 Sponsor's Efficacy Results for Key Secondary Endpoint

The key secondary efficacy variable was the change from randomization to Week 6 in the Q-LES-Q percent maximum total score. The key secondary analysis model was a mixed effect ANCOVA model with baseline Q-LES-Q percent maximum total score as a covariate, treatment as a fixed effect, and center as a random effect. Table 4 summarizes the key secondary results. None of the doses was statistically significantly different from placebo.

**Table 4. Study D1448C00001: Sponsor’s key secondary efficacy results: change from randomization to week 6 in the Q-LES-Q percent maximum total score (LOCF) in the MITT sample**

	Placebo	QTP 50mg	QTP 150mg	QTP 300mg
Sample size	158	161	160	156
LS Means	12.59	12.50	12.30	11.56
Difference from placebo (95% confidence interval)		-0.08 (-3.44, 3.28)	-0.29 (-3.66, 3.08)	-1.02 (-4.40, 2.35)
Unadjusted p-values		0.962	0.867	0.552
Adjusted p-values		1.000	1.000	1.000

(Source: d1448c00001 Study Report; Table 17, pages 90-91)

*3.1.1.4.4 Sponsor’s Other Efficacy Results*

A primary sensitivity analysis: An analysis on the change from randomization to week 6 in the MADRS total score using a mixed model for repeated measures is summarized in Table 5. The model included visit, treatment, and treatment-by-visit interaction as fixed factors, center as a random factor, and randomization MADRS total score as a covariate. Robust variance estimates of the fixed effects were used. Within subject variability was modeled using an unstructured covariance pattern. This analysis corroborates with the primary efficacy analysis using an ANCOVA model on LOCF data.

**Table 5. Study D1448C00001: Sponsor’s primary sensitivity analysis: change from randomization to week 6 in the MADRS total score (OC) in the MITT sample**

	Placebo	QTP 50mg	QTP 150mg	QTP 300mg
Sample size	178	178	168	176
LS Means	-12.14	-14.76	-15.99	-16.05
Difference from placebo (95% confidence interval)		-2.62 (-4.35, -0.89)	-3.84 (-5.42, -2.27)	-3.91 (-5.91, -1.91)
Unadjusted p-values		0.003	<0.001	<0.001

(Source: d1448c00001 Study Report; Table 11.2.1.4, page 325)

An analysis on the primary endpoint over time (LOCF): Table 6 summarizes an analysis of the change from randomization in the MADRS total score (LOCF) over time. The ANCOVA model similar to the primary analysis model was used. The responses appeared consistent over time.

**Table 6. Study D1448C00001: Sponsor’s efficacy analysis: change from randomization in the MADRS total score (LOCF) over time in the MITT sample**

	Pbo	QTP 50mg	QTP 150mg	QTP 300mg	QTP 50mg – Pbo Diff	QTP 150mg – Pbo Diff	QTP 300mg – Pbo Diff	p-value*	p-value*	p-value*
Day 4	-3.27	-4.91	-5.43	-5.35	-1.64	-2.16	-2.08	0.006	<0.001	0.001
Week 1	-6.47	-8.68	-8.35	-8.79	-2.22	-1.89	-2.32	0.001	0.006	0.001
Week 2	-9.15	-11.76	-11.68	-12.06	-2.61	-2.53	-2.91	0.001	0.002	<0.001
Week 4	-10.62	-12.53	-13.37	-12.89	-1.91	-2.75	-2.27	0.035	0.003	0.012
Week 6	-11.07	-13.56	-14.50	-14.18	-2.50	-3.44	-3.11	0.014	0.001	0.002

(Source: d1448c00001 Study Report; Table 11.2.1.3.1, pages 319-322)

\*p-values are not adjusted for multiplicity

#### *3.1.1.4.5 Reviewer's Results and Comments*

This reviewer confirmed the findings on the primary and key secondary efficacy variables as presented in Table 3 and Table 4. All three doses of quetiapine XR were superior to placebo on the change from randomization to week 6 in the MADRS total score, but not on the Q-LES-Q percent maximum score.

### **3.1.2 Study D1448C00002**

#### *3.1.2.1 Objectives*

Primary: The primary objective of this study was to evaluate the efficacy quetiapine XR versus placebo in patients with MDD by evaluation of the change from randomization to Week 6 in the MADRS total score.

Key Secondary: The key secondary objective of this study was to evaluate if quetiapine XR improved the health-related quality of life of patients with MDD, compared to placebo by assessing the change from randomization to Week 6 in the Q-LES-Q percent maximum total score (Items 1-14).

#### *3.1.2.2 Study Design*

This was an 8-week, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The study consisted of three phases. The first phase was a washout period of at least 7 days and up to 28 days. The second phase was a six-week, double-blind, randomized phase. Patients who met all eligibility criteria were randomized to receive quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine 60 mg/day, or placebo. The third phase was a two-week post-treatment follow-up period. Patients were asked to call in for discontinuation symptoms assessed by the Treatment Discontinuation Signs and Symptoms (TDSS) scale.

Male and female patients between the age of 18 and 65 years old were enrolled from April 2006 to May 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D (17-item) total score of at least 22 and HAM-D Item 1 (depressed mood) score of at least 2 both at enrollment and at randomization. Assessments of the primary endpoint, MADRS, were done on days 1, 8, 15, 29, and 43. Assessments of the key secondary endpoint, Q-LES-Q, were done on days 1, 29, and 43.

The sample size calculation was based on an 80% power and a 0.05 significant level. It was determined that 140 subjects per arm were needed to detect a 3.5-unit difference with a standard deviation of 9 for the change in the MADRS total score from randomization to week 6.

#### *3.1.2.3 Efficacy Endpoints and Analyses*

Primary endpoint and analysis: The primary endpoint was the change from randomization to Week 6 in the MADRS total score. Missing values were imputed by the LOCF method. The primary efficacy variable was analyzed by a

mixed model ANCOVA with MADRS total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

Key Secondary endpoint and analysis: The key secondary endpoint was the change in the Q-LES-Q percent maximum total score from randomization to Week 6. The short form of the Q-LES-Q consists of 16 items rated on a 5-point scale. Larger values indicate a higher perceived quality of life enjoyment and satisfaction. The Q-LES-Q total score is the sum of the first 14 items. This total score is converted to a percentage of the maximum score using the scoring conversion:

$$\text{Q-LES-Q percent maximum score} = \frac{\text{Q-LES-Q total score} - 14}{56} \times 100.$$

Missing values were imputed by the LOCF method. The key secondary endpoint was analyzed by a mixed model with Q-LES-Q percent maximum total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

A step-wise sequential testing procedure was used to handle multiple comparisons across the primary and secondary hypotheses. First, both primary hypotheses were tested. The Hommel procedure was used control the type I error rate among the two primary hypotheses. If both doses of quetiapine XR were statistically significantly superior to placebo, then the two secondary hypotheses would be tested. The Hommel procedure would also be used to control the type I error rate among the two secondary hypotheses.

#### *3.1.2.4 Efficacy Results*

##### *3.1.2.4.1 Study Population*

Subjects were enrolled from 38 centers in the United States. A total of 912 subjects were screened and 612 subjects were randomized to 1 of the four treatment groups: placebo, quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and duloxetine 60 mg/day. The disposition of the subjects is summarized in Table 7. Approximately 28% of the subjects discontinued the study prematurely. Main reasons for discontinuations were adverse events, lost to follow-up, and subjects not willing to continue. There were more adverse events in the active arms than in the placebo arm. There were also more discontinuations in the active arms than in the placebo arm.

**Table 7. Study D1448C00002: Disposition of Patients**

	Placebo (N = 157)	QTP 150mg (N = 152)	QTP 300mg (N = 152)	DUL (N = 151)	Total (N = 612)
Randomized – no treatment	0	0	0	2	2
Randomized – received treatment	157	152	152	149	610
<b>Discontinued study</b>	<b>33 (21.0)</b>	<b>52 (34.2)</b>	<b>39 (25.7)</b>	<b>46 (30.5)</b>	<b>170 (27.8)</b>
Adverse event	7 (4.5)	30 (19.7)	23 (15.1)	20 (13.1)	80 (13.1)
Condition worsened	3 (1.9)		0	2 (1.3)	5 (0.8)
Death	0	1 (0.7)	0	0	1 (0.2)
Development of study specific discontinuation criteria	1 (0.6)	1 (0.7)	1 (0.7)	1 (0.7)	4 (0.7)
Eligibility criteria not fulfilled	0	1 (0.7)	0	2 (1.3)	3 (0.5)
Other	1 (0.6)	0	1 (0.7)	2 (1.3)	4 (0.7)
Severe noncompliance	3 (1.9)	2 (1.3)	1 (0.7)	0	6 (1.0)
Subject lost to follow-up	9 (5.7)	10 (6.6)	6 (3.9)	7 (4.6)	32 (5.2)
Subject not willing to continue	9 (5.7)	7 (4.6)	7 (4.6)	12 (7.9)	35 (5.7)
<b>Completed 6-week randomized treatment phase</b>	<b>124 (79.0)</b>	<b>100 (65.8)</b>	<b>113 (74.3)</b>	<b>105 (69.5)</b>	<b>442 (72.2)</b>

(Source: d1448c00002 Study Report; Figure 3, pages 86)

The modified intent-to-treat (MITT) sample had 587 subjects. The demographics and baseline disease characteristics of the MITT sample are presented in Table 8. Patients in this study were between 18 and 65 years of age. The average age was 41 years old. There were more females than males. The majority of the subjects was Caucasian (74%) and black (21%). The distribution of the baseline MADRS total score appeared balanced across the four treatment arms.

**Table 8. Study D1448C00002: Demographic and baseline disease characteristics (MITT sample)**

	Placebo N = 152	QTP 150 mg N = 147	QTP 300 mg N = 147	DUL N = 141	Total N = 587
<i>Age (yr) n</i>					
Mean (SD)	42.3 (11.5)	40.9 (12.3)	41.6 (12.0)	40.2 (12.5)	41.3 (12.1)
Median	43.5	40.0	42.0	40.0	42.0
Min – Max	19 – 63	18 – 64	19 – 65	19 – 65	18 – 65
<i>Sex – n (%)</i>					
Male	54 (35.5)	54 (36.7)	72 (49.0)	53 (37.6)	233 (39.7)
Female	98 (64.5)	93 (63.3)	75 (51.0)	88 (62.4)	354 (60.3)
<i>Race – n (%)</i>					
Black	39 (25.7)	30 (20.4)	31 (21.1)	25 (17.7)	125 (21.3)
Caucasian	105 (69.1)	111 (75.5)	110 (74.8)	107 (75.9)	433 (73.8)
Oriental	2 (1.3)	1 (0.7)	1 (0.7)	1 (0.7)	5 (0.9)
Others	6 (4.0)	5 (3.4)	5 (3.4)	8 (5.7)	24 (4.1)
<i>Baseline MADRS-total score</i>					
Mean (SD)	30.3 (5.0)	29.8 (5.3)	30.1 (5.2)	30.4 (4.5)	30.1 (5.0)
Median	30.0	30.0	30.0	30.0	30.0
Min – Max	17 – 43	14 – 43	16 – 42	18 – 40	14 – 43

(Source: d1448c00002 Study Report; Tables 14 & 16, pages 90 & 92)

*3.1.2.4.2 Sponsor's Efficacy Results for Primary Endpoint*

The primary efficacy variable was the change from randomization to Week 6 in the MADRS total score. The primary analysis model was a mixed effect ANCOVA model with baseline MADRS total score as a covariate, treatment as a fixed factor, and center as a random effect. Multiple hypotheses were tested sequentially. First the two primary hypotheses were tested using the Hommel procedure. If both primary hypotheses were significant, then the two secondary hypotheses were tested using the Hommel procedure. The primary analysis is summarized in Table 9. Both doses of quetiapine XR were statistically significantly different from placebo.

**Table 9. Study D1448C00002: Sponsor's primary efficacy results: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg	DUL
Sample size	152	147	147	141
LS Means	-11.18	-14.81	-15.29	-14.64
Difference from placebo (95% confidence interval)		-3.63 (-5.73, -1.53)	-4.11 (-6.21, -2.01)	-3.46 (-5.59, -1.34)
Unadjusted p-values		0.001	<0.001	0.002
Adjusted p-values		0.001	<0.001	Not done

(Source: d1448c00001 Study Report; Table 18, pages 98)

*3.1.2.4.3 Sponsor's Efficacy Results for Key Secondary Endpoint*

The key secondary efficacy variable was the change from randomization to Week 6 in the Q-LES-Q percent maximum total score. The key secondary analysis model was a mixed effect ANCOVA model with baseline Q-LES-Q percent maximum total score as a covariate, treatment as a fixed effect, and center as a random effect. Table 10 summarizes the key secondary results. None of the doses was statistically significantly different from placebo.

**Table 10. Study D1448C00002: Sponsor's key secondary efficacy results: change from randomization to week 6 in the Q-LES-Q percent maximum total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg	DUL
Sample size	144	136	141	129
LS Means	11.26	13.68	13.59	16.69
Difference from placebo (95% confidence interval)		2.42 (-1.41, 6.26)	2.33 (-1.46, 6.12)	5.43 (1.54, 9.31)
Unadjusted p-values		0.215	0.227	0.006
Adjusted p-values		0.227	0.227	Not done

(Source: d1448c00002 Study Report; Table 32, pages 114)

*3.1.1.4.4 Sponsor's Other Efficacy Results*

A primary sensitivity analysis: An analysis on the change from randomization to week 6 in the MADRS total score using a mixed model for repeated measures is summarized in Table 11. The model included treatment, visit, and treatment-by-visit interaction as fixed effects, center as random effect, and baseline MADRS total score as a covariate. Robust variance estimates for the fixed effects were

used to test the treatment differences. The within subject variance was unstructured. This analysis corroborates with the primary efficacy analysis using an ANCOVA model on LOCF data.

**Table 11. Study D1448C00002: Sponsor’s primary sensitivity analysis: change from randomization to week 6 in the MADRS total score (OC) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg	DUL
Sample size	152	147	147	141
LS Means	-11.69	-15.87	-16.29	-16.23
Difference from placebo		-4.18	-4.60	-4.54
(95% confidence interval)		(-5.91, -2.45)	(-6.64, -2.26)	(-6.68, -2.41)
Unadjusted p-values		<0.001	<0.001	<0.001

(Source: d1448c00002 Study Report; Table 11.2.1.4, page 335)

An analysis on the primary endpoint over time (LOCF): Table 12 summarizes an analysis of the change from randomization in the MADRS total score (LOCF) over time. The ANCOVA model similar to the primary analysis model was used. The responses appeared consistent over time.

**Table 12. Study D1448C00002: Sponsor’s efficacy analysis: change from randomization in the MADRS total score (LOCF) over time in the MITT sample**

	Pbo	QTP 150mg	QTP 300mg	DUL	QTP 150mg – Pbo Diff	p-value*	QTP 300mg – Pbo Diff	p-value*	DUL - Pbo Diff	p-value*
Week 1	-6.01	-8.36	-8.19	-6.81	-2.35	0.002	-2.17	0.004	-0.79	0.301
Week 2	-9.03	-12.43	-11.34	-10.95	-3.40	<0.001	-2.31	0.009	-1.92	0.031
Week 4	-10.39	-14.22	-13.65	-13.17	-3.84	<0.001	-3.26	0.001	-2.79	0.005
Week 6	-11.18	-14.81	-15.29	-14.64	-3.63	0.001	-4.11	<0.001	-3.46	0.002

(Source: d1448c00002 Study Report; Table 11.2.1.3.1, pages 327-330)

\*p-values are not adjusted for multiplicity

#### 3.1.2.4.5 Reviewer’s Results and Comments

This reviewer confirmed the findings on the primary and key secondary efficacy variables as presented in Table 9 and Table 10. Both doses of quetiapine XR were superior to placebo on the change from randomization to week 6 in the MADRS total score, but not on the Q-LES-Q percent maximum score.

### 3.1.3 Study D1448C00003

#### 3.1.3.1 Objectives

Primary: The primary objective of this study was to evaluate the efficacy quetiapine XR versus placebo in patients with MDD by evaluation of the change from randomization to Week 8 in the MADRS total score.

Key Secondary: The key secondary objective of this study was to evaluate if quetiapine XR improved the health-related quality of life in patients with MDD, compared to placebo by assessing the change from randomization to Week 8 in the Q-LES-Q percent maximum total score (Items 1-14).

### 3.1.3.2 Study Design

This was a 10-week, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized, modified fixed-dosed study. The study consisted of three phases. The first phase was an enrollment period of at least 7 days and up to 28 days. The second phase was an eight-week, double-blind, randomized phase. Patients who met all eligibility criteria were randomized to either quetiapine XR 150 mg/day or placebo. After 2 weeks of treatment, patients with an inadequate response (defined as failure to achieve at least 20% improvement from randomization in MADRS total score) were up-titrated to 300 mg/day or matching placebo. The third phase was a two-week post-treatment follow-up period. Patients were asked to complete the TDSS assessment for drug discontinuation signs and symptoms.

Male and female patients between the age of 18 and 65 years old were enrolled from April 2006 to May 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D (17-item) total score of at least 22 and HAM-D Item 1 (depressed mood) score of at least 2 both at enrollment and at randomization. Assessments of the primary endpoint, MADRS, were done on days 1, 8, 15, 29, 43, and 57. Assessments of the key secondary endpoint, Q-LES-Q, were done on days 1, 29, and 57.

The sample size calculation was based on a 90% power and a 0.05 significant level. It was determined that 140 subjects per arm were needed to detect a 3.5-unit difference with a standard deviation of 9 for the change in the MADRS total score from randomization to week 6.

### 3.1.3.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from randomization to Week 8 in the MADRS total score. Missing values were imputed by the LOCF method. The primary efficacy variable was analyzed by a mixed model ANCOVA with MADRS total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

Key Secondary endpoint and analysis: The key secondary endpoint was the change in the Q-LES-Q percent maximum total score from randomization to Week 8. The short form of the Q-LES-Q consists of 16 items rated on a 5-point scale. Larger values indicate a higher perceived quality of life enjoyment and satisfaction. The Q-LES-Q total score is the sum of the first 14 items. This total score is converted to a percentage of the maximum score using the scoring conversion:

$$\text{Q-LES-Q percent maximum score} = \frac{\text{Q-LES-Q total score} - 14}{56} \times 100.$$

Missing values are imputed by the LOCF method. The key secondary endpoint was analyzed by a mixed model with Q-LES-Q percent maximum total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

A step-wise sequential testing procedure was used to handle multiple comparisons between the primary and secondary hypotheses. First, the primary outcome variable was tested. If it was statistically significant, then the secondary outcome variable was tested.

### 3.1.3.4 Efficacy Results

#### 3.1.3.4.1 Study Population

Subjects were enrolled from 36 centers in the United States. A total of 513 subjects were screened and 310 subjects were randomized to quetiapine XR 150/300 mg/day, or placebo. Initially, subjects receiving quetiapine XR were titrated to 150 mg/day. If the treatment yielded inadequate responses, then patients were up-titrated to 300 mg/day. The disposition of the subjects is summarized in Table 13. Approximately 29% of the subjects discontinued prematurely. Main reasons for discontinuation were adverse events, lack of therapeutic response, lost to follow-up, and not willing to continue. There were more adverse events in the quetiapine XR arm than in the placebo arm.

**Table 13. Study D1448C00003: Disposition of patients**

	Placebo (N = 156)	QTP 150/300 mg (N = 154)	Total (N = 310)
Randomized, not treated	1	2	3
Randomized, treated	155	152	307
<b>Discontinued the study: N (%)</b>	<b>45 (28.8)</b>	<b>46 (29.9)</b>	<b>91 (29.4)</b>
Adverse event	4 (2.6)	13 (8.4)	17 (5.5)
Eligibility criteria not fulfilled	1 (0.6)	2 (1.3)	3 (1.0)
Lack of therapeutic response	7 (4.5)	7 (4.5)	14 (4.5)
Other	3 (1.9)		3 (1.0)
Severe noncompliance to protocol	3 (1.9)	1 (0.6)	4 (1.3)
Did not complete $\geq 50$ days of treatment	1 (0.6)		1 (0.3)
Lost to follow-up	12 (7.7)	11 (7.1)	23 (7.4)
Not willing to continue the study	14 (9.0)	12 (7.8)	26 (8.4)
<b>Completed 8-week randomized treatment period</b>	<b>111 (71.2)</b>	<b>108 (70.1)</b>	<b>219 (70.6)</b>

(Source: d1448c00003 Study Report; Figure 2, page 81)

The modified intent-to-treat (MITT) sample had 299 subjects. The demographics and baseline disease characteristics of the MITT sample are presented in Table 14. Patients in this study were between 18 and 65 years of age. The average age was 43 years old. There were more females than males. The majority of the subjects was Caucasian (67%) and black (27%). The distribution of the baseline MADRS total score appeared similar between the two treatment arms.

**Table 14. Study D1448C00003: Demographic and baseline disease characteristics (MITT sample)**

	Placebo N = 152	QTP 150/300 mg N = 147	Total N = 299
<i>Age (yr) n</i>			
Mean (SD)	42.6 (11.7)	43.3 (10.5)	42.9 (11.1)
Median	44.0	45.0	45.0
Min – Max	18 – 64	19 – 61	18 – 64
<i>Sex – n (%)</i>			
Male	54 (35.5)	52 (35.4)	106 (35.5)
Female	98 (64.5)	95 (64.6)	193 (64.5)
<i>Race – n (%)</i>			
Black	42 (27.6)	40 (27.2)	82 (27.4)
Caucasian	100 (65.8)	101 (68.7)	201 (67.2)
Oriental	3 (2.0)	0 (0.0)	3 (1.0)
Others	7 (4.6)	6 (4.1)	13 (4.4)
<i>Baseline MADRS-total score</i>			
Mean (SD)	29.3 (5.3)	29.7 (6.2)	29.5 (5.8)
Median	30.0	30.0	30.0
Min – Max	15 – 44	13 – 48	13 – 48

(Source: d1448c00003 Study Report; Tables 14 & 16, pages 84-85 & 87)

Patients who failed to achieve adequate response (defined as at least 20% reduction in the MADRS total score from randomization after two weeks of treatment) had their doses up-titrated to 300 mg/day. The sponsor reported 35 subjects (23.0%) in the placebo arm and 22 subjects (15.0%) in the quetiapine arm did not achieve adequate response after two weeks of treatment. However, when examining the change from baseline in the MADRS total score at week 2, this reviewer found that there were 39 subjects (25.7%) in the placebo arm and 28 subjects (19.0%) in the quetiapine arm who failed to achieve at least 20% reduction in the MADRS total score from randomization.

#### 3.1.3.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from randomization to Week 8 in the MADRS total score. The primary analysis model was a mixed effect ANCOVA model with baseline MADRS total score as a covariate, treatment as a fixed factor, and center as a random effect. The primary analysis is summarized in Table 15. Quetiapine XR was statistically significantly superior to placebo in the change from randomization to week 8 in the MADRS total score.

**Table 15. Study D1448C00003: Sponsor’s primary efficacy results: change from randomization to week 8 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150/300 mg
Sample size	152	147
LS Means	-13.10	-16.49
Difference from placebo (95% confidence interval)		-3.39 (-5.48, -1.30)
Unadjusted p-values		0.002
Adjusted p-values		0.002

(Source: d1448c00003 Study Report; Table 18, pages 92)

*3.1.3.4.3 Sponsor’s Efficacy Results for Key Secondary Endpoint*

The key secondary efficacy variable was the change from randomization to Week 8 in the Q-LES-Q percent maximum total score. The key secondary analysis model was a mixed effect ANCOVA model with baseline Q-LES-Q percent maximum total score as a covariate, treatment as a fixed effect, and center as a random effect. Table 16 summarizes the key secondary results. Quetiapine XR was not statistically significantly superior to placebo.

**Table 16. Study D1448C00003: Sponsor’s key secondary efficacy results: change from randomization to week 8 in the Q-LES-Q percent maximum total score (LOCF) in the MITT sample**

	Placebo	QTP 150/300 mg
Sample size	137	138
LS Means	11.93	13.80
Difference from placebo (95% confidence interval)		1.87 (-1.76, 5.50)
Unadjusted p-values		0.311

(Source: d1448c00003 Study Report; Table 29, pages 105)

*3.1.3.4.4 Sponsor’s Other Efficacy Results*

A primary sensitivity analysis: An analysis on the change from randomization to week 8 in the MADRS total score using a mixed model for repeated measures is summarized in Table 17. The model included visit, treatment, and treatment-by-visit interaction as fixed factors, center as a random factor, and randomization MADRS total score as a covariate. Robust variance estimates of the fixed effects were used for testing treatment differences. The model used an unstructured covariance pattern. This analysis corroborates with the primary efficacy analysis using an ANCOVA model on LOCF data.

**Table 17. Study D1448C00003: Sponsor’s primary sensitivity analysis: change from randomization to week 8 in the MADRS total score (OC) in the MITT sample**

	Placebo	QTP 150/300 mg
Sample size	152	147
LS Means	-14.26	-18.12
Difference from placebo (95% confidence interval)		-3.87 (-6.02, -1.71)
Unadjusted p-values		<0.001

(Source: d1448c00003 Study Report; Table 11.2.1.1.3, page 266)

An analysis on the primary endpoint over time (LOCF): Table 18 summarizes an analysis of the change from randomization in the MADRS total score (LOCF) over time. The ANCOVA model similar to the primary analysis model was used. Quetiapine XR showed numerically consistently better responses than placebo over time.

**Table 18. Study D1448C00003: Sponsor’s efficacy analysis: change from randomization in the MADRS total score (LOCF) over time in the MITT sample**

	Pbo	QTP 150/300mg	QTP - Pbo Diff	p-value*
Week 1	-7.29	-9.22	-1.93	0.010
Week 2	-9.96	-12.64	-2.68	0.004
Week 4	-11.62	-14.07	-2.45	0.011
Week 6	-13.22	-15.57	-2.36	0.021
Week 8	-13.10	-16.49	-3.39	0.002

(Source: d1448c00003 Study Report; Table 11.2.1.1.1, pages 258-261)

\*p-values are not adjusted for multiplicity

#### 3.1.3.4.5 Reviewer’s Results and Comments

This reviewer confirmed the findings on the primary and key secondary efficacy variables as presented in Table 15 and Table 16. Quetiapine XR was superior to placebo on the change from randomization to week 8 in the MADRS total score, but not on the Q-LES-Q percent maximum score.

### 3.1.4 Study D1448C00005

#### 3.1.4.1 Objectives

Primary: The primary objective of the study was to evaluate the efficacy of quetiapine XR compared with placebo in the time from randomization to a depressed event in patients with MDD.

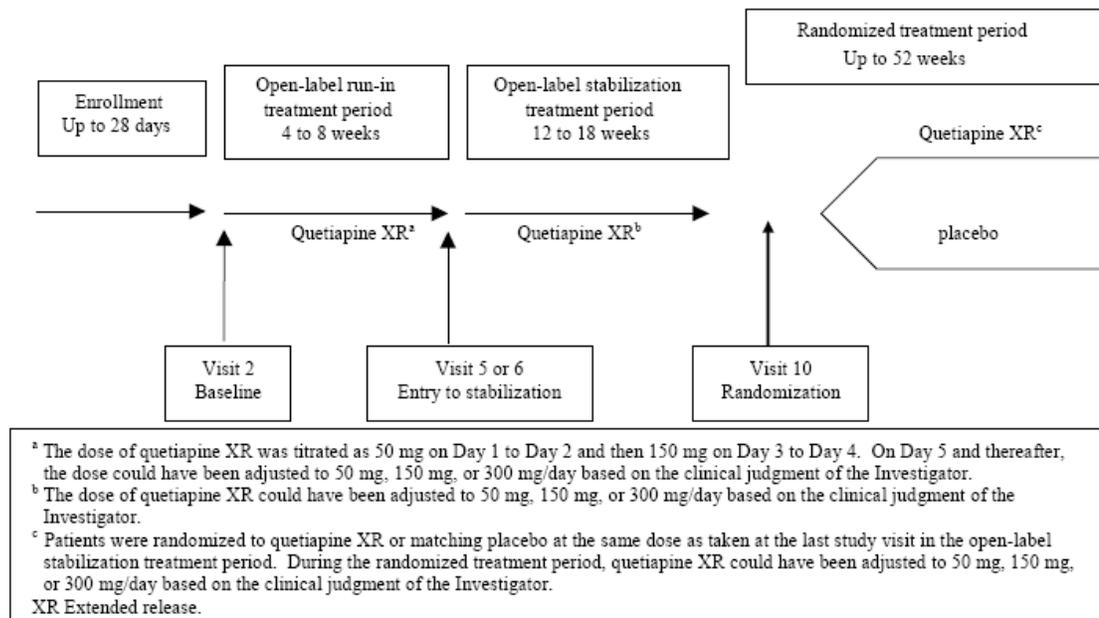
A depressed event is defined as fulfilling at least one of the following:

- Initiation of pharmacological treatment by the investigator, other than the allowed hypnotics, to treat depressive symptoms.
- Initiation of pharmacological treatment by the patient for at least 1 week, other than the allowed hypnotics, to treat depressive symptoms.
- Hospitalization for depressive symptoms.

- d. MADRS > 18 at 2 consecutive assessments 1 week apart or at the final assessment if the patient discontinues.
- e. Clinical Global Impressive-Severity of Illness (CGI-S) of at least 5.
- f. Suicide attempt or discontinuation from study due to imminent risk of suicide.

### 3.1.4.2 Study Design

This was a multi-center, randomized-withdrawal, parallel-group, double-blind, placebo-controlled study. The study consisted of 4 periods: enrollment (up to 28 days), an open-label run-in treatment period (4 to 8 weeks), an open-label stabilization treatment period (12 to 18 weeks), and a double-blind, randomized treatment period (up to 52 weeks). During the open-label stabilization period, patients were treated with open-label quetiapine XR for at least 12 weeks. The dosage could be adjusted to 50, 150, or 300 mg/day to maximize efficacy and tolerability. Patients must have responded to acute treatment during the open-label treatment phase in order to be eligible to continue maintenance treatment during the randomized treatment phase. Eligible patients would be randomized to continue quetiapine XR or switch to placebo for up to 52 weeks. The dosage could be adjusted to 50, 150, or 300 mg/day as clinically indicated during the study. The study flow chart is summarized in Figure 2.



**Figure 2. Study D1448C00005: Flow chart**

(Source: d1448c00005 Study Report; Figure 1, page 41)

Male and female patients between the age of 18 and 65 years old were enrolled from December 2005 to August 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D (17-item) total score of at least 20 and HAM-D Item 1 (depressed mood) score of at least 2 both at enrollment. Key entry criteria are summarized in Table 19.

**Table 19. Study D1448C00005: Key entry criteria**

Entry criteria <sup>a</sup>	Enrollment entry	Entry to OLST		Entry to randomization (Day of randomization)
		(Week 4 or 8 of OLT)	During OLST	
HAM-D total score	≥20			
HAM-D Item 1	≥2			
MADRS		≤12	≤14	≤12
CGI-S		≤3	≤4	≤3

<sup>a</sup> See additional entry and exclusion criteria, Sections 5.3.1 and 5.3.2.

CGI-S Clinical Global Impression-Severity of Illness. HAM-D Hamilton Rating Scale for Depression.

MADRS Montgomery-Åsberg Depression Rating Scale. OLT Open-label run-in treatment.

OLST Open-label stabilization treatment.

(Source: d1448c00005 Study Report; Table 2, page 42)

The sample size for this study was calculated based on an 85% power assuming a hazard ratio of 0.55. It was estimated that 101 depressed events were required in the quetiapine XR and placebo groups.

#### 3.1.4.3 Efficacy Endpoints and Analyses

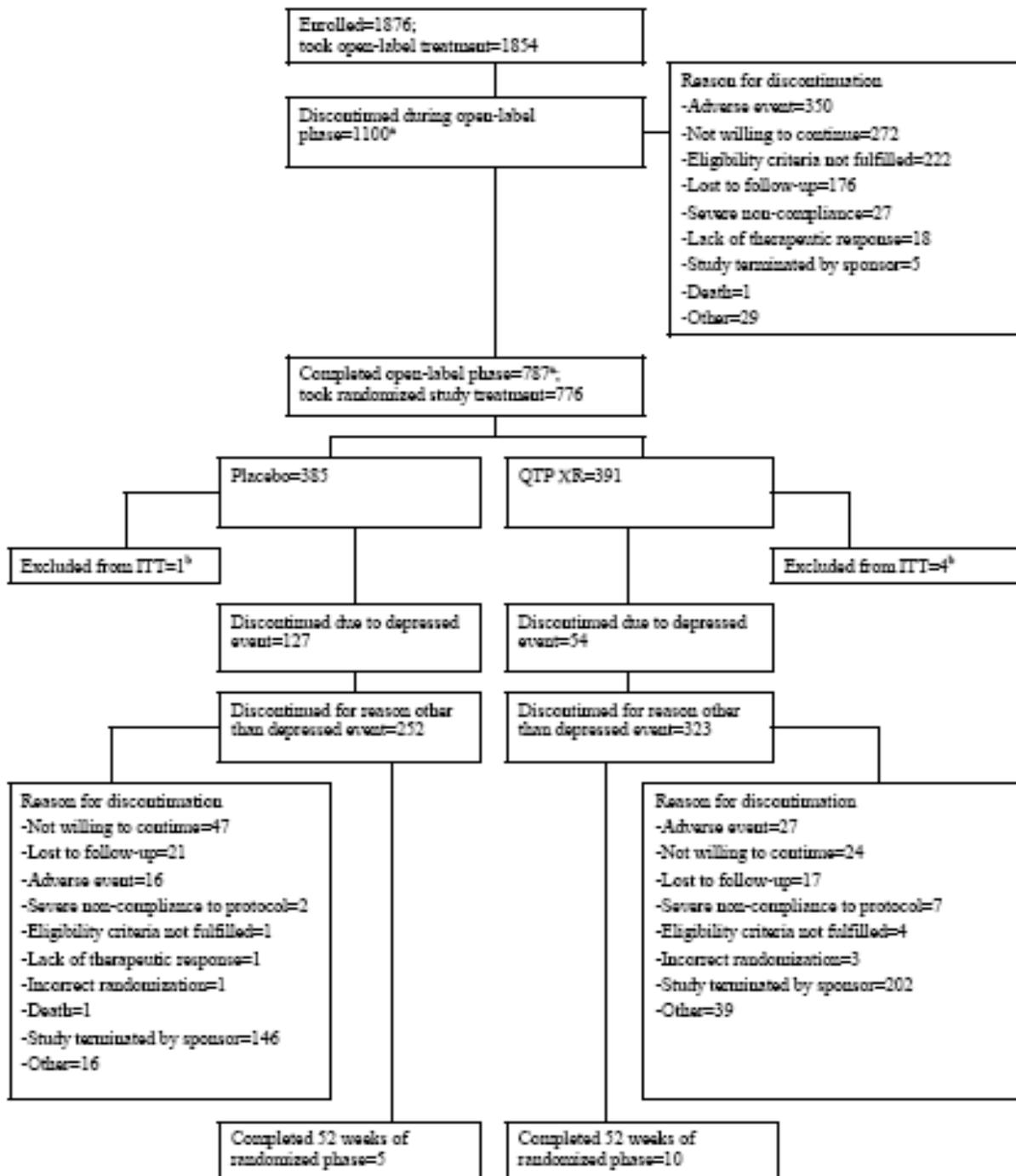
**Primary endpoint and analysis:** The primary efficacy variable was the time from randomization to an occurrence of a depressed event. A depressed event was defined in section 3.1.4.1. The time to a depressed event was analyzed by a Cox proportional hazards model. The null hypothesis of equality between the two arms was tested by a 2-sided Wald test. Region (U.S. versus non-U.S.) was included as a stratification variable in the analysis.

#### 3.1.4.4 Efficacy Results

##### 3.1.4.4.1 Study Population

Subjects were enrolled from Bulgaria (6 sites), Canada (10 sites), Finland (5 sites), France (10 sites), Germany (9 sites), Romania (5 sites), Russia (7 sites), Slovakia (8 sites), South Africa (4 sites), U.K. (9 sites), and U.S.A (164 sites). A total of 2883 subjects were screened and 1876 subjects enrolled. The randomized sample consisted of 787 subjects and 776 subjects received treatment.

The disposition of the patients is summarized in Figure 3. In the randomized treatment period, excluding subjects who discontinued due to depressed events, the main reasons for discontinuation were not willing to continue, adverse events, and lost to follow-up. Only 15 patients completed the 52 weeks randomized phase.



\* This number includes 11 patients who were assigned a randomization number, but did not receive randomized study treatment.

<sup>b</sup> All 5 patients from Site 1047 (1 patient in the placebo group and 4 patients in the quetiapine XR group) were excluded from the ITT population because the site was not compliant with GCP and the integrity of the data pertaining to these patients could not be verified.

**Figure 3. Study D1448C00005: Disposition of patients**

The intent-to-treat (ITT) sample consisted of 771 subjects. The demographics and baseline disease characteristics of the ITT sample are presented in Table 20. Patients in this study were between 19 and 65 years of age. The average age was

45 years old. The ratio of female to male was approximately 2 to 1. The majority of the subjects was Caucasian (88%) and black (9%).

**Table 20. Study D1448C00005: Demographic and baseline disease characteristics (ITT sample)**

	Placebo N = 384	QTP XR N = 387	Total N = 771
<i>Age (yr) n</i>			
Mean (SD)	43.8 (11.5)	45.4 (11.2)	44.6 (11.4)
Median	46.0	47.0	46.0
Min – Max	19 – 65	19 – 65	19 – 65
<i>Sex – n (%)</i>			
Male	130 (33.9)	132 (34.1)	262 (34.0)
Female	254 (66.1)	255 (65.9)	509 (66.0)
<i>Race – n (%)</i>			
Black	37 (9.6)	33 (8.5)	70 (9.1)
Caucasian	339 (88.3)	336 (86.8)	675 (87.6)
Oriental	3 (0.8)	2 (0.5)	5 (0.7)
Others	5 (1.3)	16 (4.1)	21 (2.7)
<i>Enrollment MADRS-total score</i>			
Mean (SD)	27.7 (5.8)	28.6 (5.9)	28.2 (5.9)
Median	28.0	29.0	28.0
Min – Max	4 – 44	9 – 45	4 – 45
<i>Randomization MADRS-total score</i>			
Mean (SD)	5.3 (3.7)	5.8 (3.6)	5.5 (3.7)
Median	5.0	6.0	6.0
Min – Max	4 – 12	0 – 12	0 – 12

(Source: d1448c00005 Study Report; Tables 18 & 19, pages 113 & 115)

#### 3.1.4.4.2 Sponsor’s Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from randomization to a depressed event. The primary efficacy variable was analyzed by a Cox proportional hazard model with U.S. as a stratification factor. The Wald’s test was used to test the difference between quetiapine XR and placebo. The results are presented in Table 21. Quetiapine XR flexible dose (50 mg/day, 150 mg/day, or 300 mg/day) significantly increased the time to a depressed event compared with placebo.

**Table 21. Study D1448C00005: Sponsor’s primary efficacy analysis: Time to depressed event (ITT sample). Wald’s test, comparison of QTP XR versus Placebo with Cox Regression**

	Placebo (N=384)	QTP XR (N=387)
Numbers of relapses (%)	132 (34.4)	55 (14.2)
Comparison between treatment groups		
Hazard ratio		0.34
95% confidence interval		(0.25, 0.46)
p-value		< 0.001

(Source: Clinical Study Report: Study d1448C00005; Table 22, page 122)

3.1.4.4.3 Sponsor's Other Efficacy Results

**Primary sensitivity analysis (primary analysis on per-protocol sample):** The primary efficacy variable was analyzed using the per-protocol (PP) sample. The same Cox model as in the primary analysis was used. The results are summarized in Table 22. This analysis corroborates with the primary analysis.

**Table 22. Study D1448C00005: Sponsor's primary sensitivity analysis: Time to depressed event (PP sample). Wald's test, comparison of QTP XR versus Placebo with Cox Regression**

	Placebo (N=290)	QTP XR (N=303)
Numbers of relapses (%)	92 (31.7)	39 (12.9)
Comparison between treatment groups		
Hazard ratio		0.33
95% confidence interval		(0.23, 0.49)
p-value		<0.001

(Source: Clinical Study Report: Study d1448C00005; Table 11.2.1.1.5, page 588)

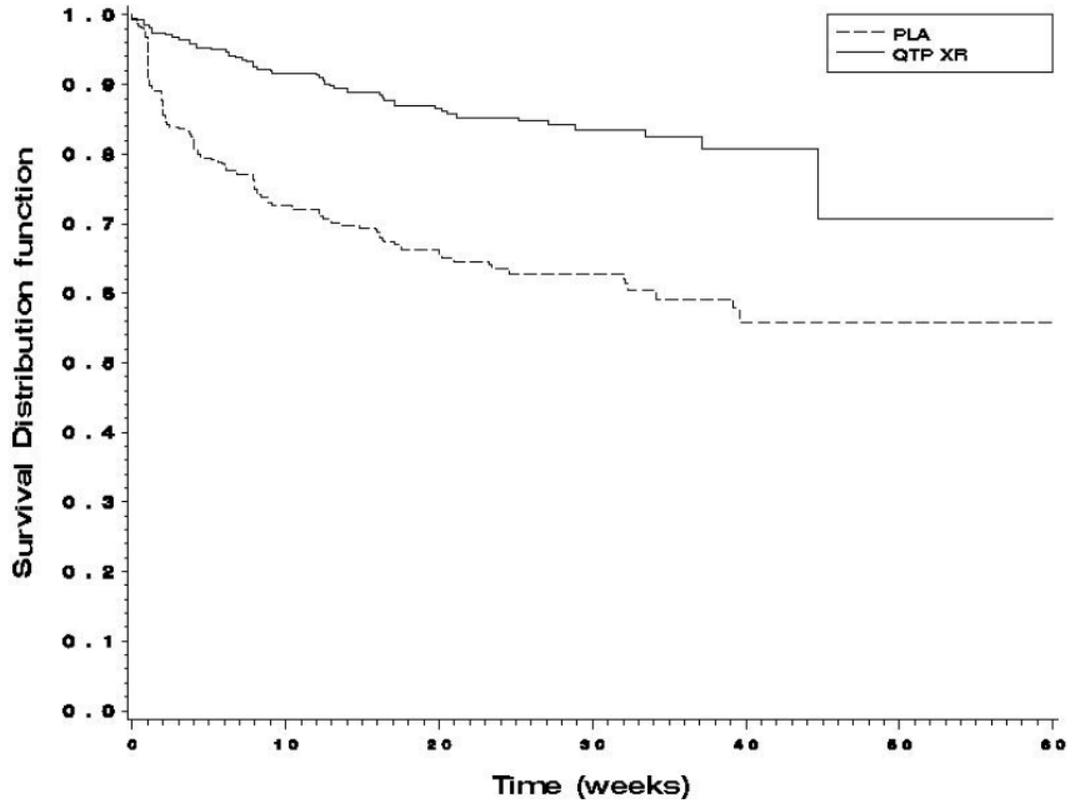
**Primary sensitivity analysis (excluding events occurred up to 30 days after randomization):** To ensure the depressed events were not due to the immediate effects of treatment discontinuation, the primary efficacy variable was reanalyzed excluding all events occurred up to 30 days after randomization. For this analysis, all events that occurred in the first 29 days after randomization were censored. Table 23 summarizes the results. This analysis also corroborates with the primary analysis.

**Table 23. Study D1448C00005: Sponsor's primary sensitivity analysis: Time to depressed event (ITT sample), excluding events occurred up to first 30 days after randomization. Wald's test, comparison of QTP XR versus Placebo with Cox Regression**

	Placebo (N=384)	QTP XR (N=387)
Numbers of relapses (%)	59 (15.4)	39 (10.1)
Comparison between treatment groups		
Hazard ratio		0.49
95% confidence interval		(0.33, 0.73)
p-value		0.001

(Source: Clinical Study Report: Study d1448C00005; Table 11.2.1.1.1, page 584)

**Kaplan-Meier curves for time to a depressed event:** The Kaplan-Meier curves for time to a depressed event are presented in Figure 4 showing a separation between quetiapine XR and placebo.

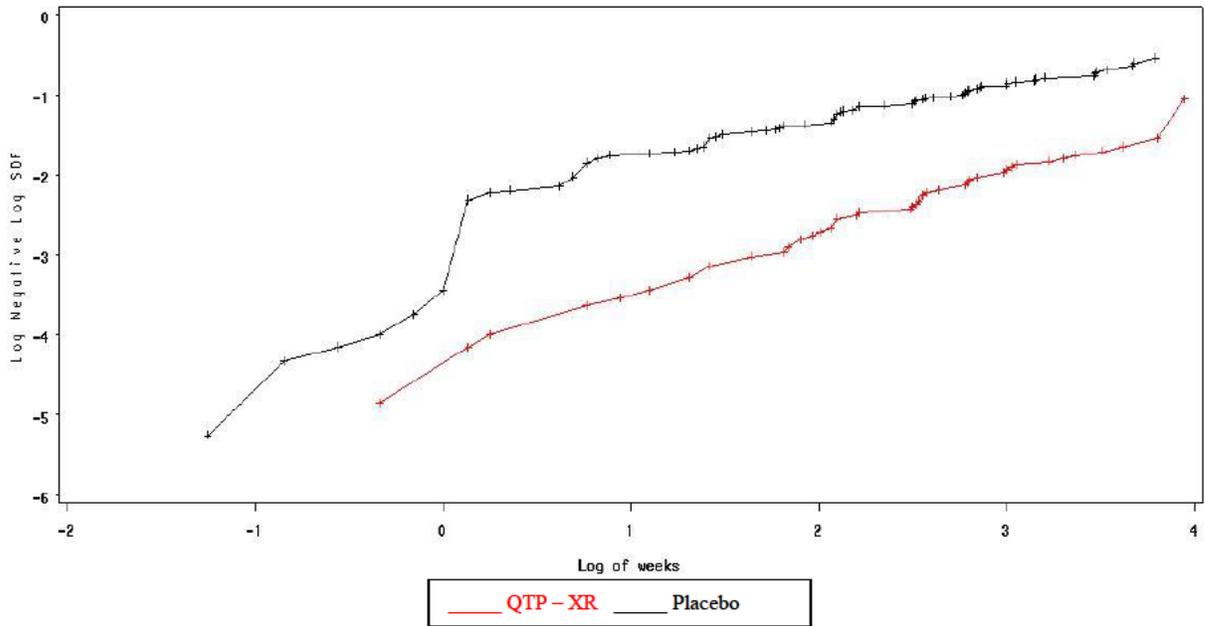


**Figure 4. Study D1448C00005: Time to a depressed event, Kaplan-Meier Curves (ITT sample)**  
 (Source: Clinical Study Report: Study d1448C00005; Figure 4, page 123)

*3.1.4.4 Reviewer’s Results and Comments*

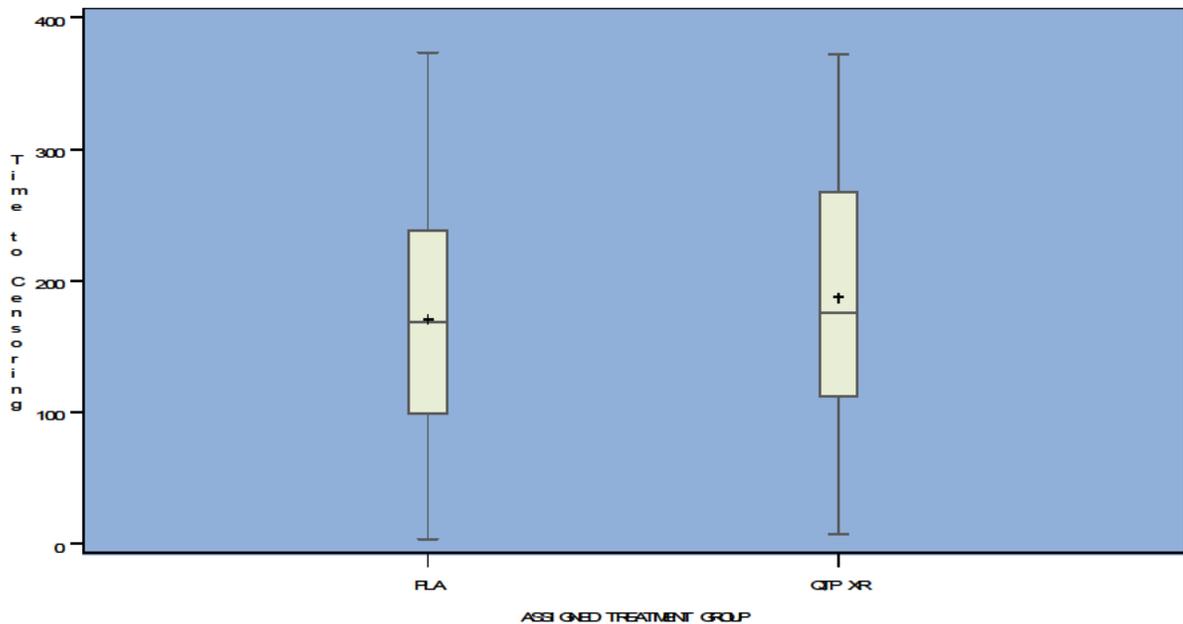
This reviewer confirms the sponsor’s finding on the primary efficacy endpoint presented in Table 21. Quetiapine XR statistically significantly increased the time to a depressed event.

The Cox model relies on the proportional hazard assumption. To examine this assumption, a log(-log (survival )) curve was produced. Figure 5 plots the log(-log(survival (week))) versus log(week). The proportional hazard assumption is reasonable when the two curves are parallel. Figure 5 suggests that the proportional hazard assumption is reasonable for this study.



**Figure 5. Study D1448C00005: Log(-Log(Survival)) Curve (ITT sample)**  
 (Source: Reviewer's result)

Figure 6 plots the time to censoring for the quetiapine and placebo groups. The quetiapine group has a slightly longer time to censoring than the placebo group.



**Figure 6. Study D1448C00005: Time to Censoring**  
 (Source: Reviewer's result)

In the intent-to-treat (ITT) sample, the sponsor excluded 5 subjects from site # 1047 due to non-compliance. Four subjects came from the quetiapine XR group and 1 from the placebo. As a sensitivity analysis, this reviewer classified the four

subjects from the quetiapine XR group as events and kept the subject from the placebo arm as censor. A Cox regression model similar to the primary analysis was performed. The results are presented in Table 24 and are supportive of the primary analysis.

**Table 24. Study D1448C00005: Reviewer’s sensitivity efficacy analysis: Time to depressed event (ITT sample). Wald’s test, comparison of QTP XR versus Placebo with Cox Regression**

	Placebo (N=385)	QTP XR (N=391)
Numbers of relapses (%)	132 (34.3)	59 (15.1)
Comparison between treatment groups		
Hazard ratio		0.36
95% confidence interval		(0.27, 0.49)
p-value		< 0.001

(Source: Reviewer’s results)

### 3.1.5 Study D1448C00006

#### 3.1.5.1 Objectives

**Primary:** The primary objective of the study was to evaluate the efficacy of quetiapine XR in combination with an antidepressant versus an antidepressant in combination with placebo in patients with Major Depressive Disorder (MDD) who have had an inadequate response to antidepressant monotherapy.

**Key Secondary:** The key secondary objective of this study was to evaluate if quetiapine XR in combination with an antidepressant improved the health-related quality of life in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo by assessing the change from randomization to Week 6 in the Q-LES-Q percent maximum total score (Items 1-14).

#### 3.1.5.2 Study Design

This was an 8-week, multi-center, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The study consisted of three periods. The first period was an enrollment period of up to 14 days. The second period was a six-week, double-blind, randomized phase. Patients who met all eligibility criteria were randomized to receive quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, or placebo in combination with the ongoing antidepressant treatment. The third period was a two-week post-treatment follow-up period. Patients were asked to call in for discontinuation symptoms assessed by the Treatment Discontinuation Signs and Symptoms (TDSS) scale.

Male and female patients between the age of 18 and 65 years old were enrolled from April 2006 to July 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D (17-item) total score of at least 20 and HAM-D Item 1 (depressed mood) score of

at least 2 both at enrollment and at randomization. Patients should have been on treatment with antidepressants for at least 6 weeks prior to enrollment (at least minimum effective antidepressant dose according to the prescribing information), with at least 1 dose increase when permitted according to the prescribing information. Assessments of the primary endpoint, MADRS, were done on days 1, 8, 15, 29, and 43. Assessments of the key secondary endpoint, Q-LES-Q, were done on days 1, 29, and 43.

The sample size calculation was based on a 90% power and a 0.05 significant level. It was determined that 140 subjects per arm were needed to detect a 3.5-unit difference with a standard deviation of 9 for the change in the MADRS total score from randomization to week 6.

### *3.1.5.3 Efficacy Endpoints and Analyses*

Primary endpoint and analysis: The primary endpoint was the change from randomization to Week 6 in the MADRS total score. Missing values were imputed by the LOCF method. The primary efficacy variable was analyzed by a mixed model ANCOVA with MADRS total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

Key Secondary endpoint and analysis: The key secondary endpoint was the change in the Q-LES-Q percent maximum total score from randomization to Week 6. The short form of the Q-LES-Q consists of 16 items rated on a 5-point scale. Larger values indicate a higher perceived quality of life enjoyment and satisfaction. The Q-LES-Q total score is the sum of the first 14 items. This total score is converted to a percentage of the maximum score using the scoring conversion:

$$\text{Q-LES-Q percent maximum score} = \frac{\text{Q-LES-Q total score} - 14}{56} \times 100.$$

Missing values were imputed by the LOCF method. The key secondary endpoint was analyzed by a mixed model with Q-LES-Q percent maximum total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

A step-wise sequential testing procedure was used to handle multiple comparisons across the primary and secondary hypotheses. First, both primary hypotheses were tested. The Hommel procedure was used to control the type I error rate between the two primary hypotheses. If both doses of quetiapine XR were statistically significantly superior to placebo, then the two secondary hypotheses would be tested. The Hommel procedure would also be used to control the type I error rate between the two secondary hypotheses.

### 3.1.5.4 Efficacy Results

#### 3.1.5.4.1 Study Population

Subjects were enrolled from 53 centers in the United States. A total of 659 subjects were screened and 446 subjects were randomized to 1 of the three treatment groups: placebo, quetiapine XR 150 mg/day, quetiapine XR 300 mg/day in combination with an antidepressant. The disposition of the subjects is summarized in Table 25. In Table 25 and all subsequent tables of this study, placebo, QTP 150 mg, QTP 300 mg are used to denote placebo, quetiapine XR 150 mg/day, quetiapine XR 300 mg/day in combination with an antidepressant. Both quetiapine XR groups had more patients who discontinued the study prematurely than the placebo group. Main reasons for patients to discontinue were adverse events, lost to follow-up, and patients not willing to continue. There were more adverse events in the two quetiapine XR groups than in the placebo group.

**Table 25. Study D1448C00006: Disposition of patients**

	Placebo (N = 148)	QTP 150mg (N = 148)	QTP 300mg (N = 150)	Total (N = 446)
Randomized (not treated)	0	0	1	1
Randomized (treated)	148	148	149	445
<b>Discontinued study: n (%)</b>	<b>23 (15.5)</b>	<b>34 (23.0)</b>	<b>45 (30.0)</b>	<b>102 (22.9)</b>
Adverse event	1 (0.7)	16 (10.8)	27 (18.0)	44 (9.9)
Eligibility criteria not fulfilled		1 (0.7)	1 (0.7)	2 (0.4)
Lack of therapeutic response	4 (2.7)	2 (1.4)		6 (1.3)
Severe non-compliance with the study protocol		2 (1.4)		2 (0.4)
Did not complete $\geq$ 36 days of study treatment		1 (0.7)	1 (0.7)	2 (0.4)
Lost to follow-up	10 (6.8)	8 (5.4)	7 (4.7)	25 (5.6)
Patients not willing to continue	8 (5.4)	4 (2.7)	6 (4.0)	18 (4.0)
Other			3 (2.0)	3 (0.7)
<b>Completed 6-week randomized treatment period: n (%)</b>	<b>125 (84.5)</b>	<b>114 (77.0)</b>	<b>105 (70.0)</b>	<b>344 (77.1)</b>

(Source: d1448c00006 Study Report; Figure 3, page 92)

The modified intent-to-treat (MITT) sample had 432 subjects. The demographics and baseline disease characteristics of the MITT sample are presented in Table 26. Patients in this study were between 19 and 65 years of age. The average age was 45 years old. The ratio of female to male was more than 2 to 1. The majority of the subjects was Caucasian (90%). The distribution of the baseline MADRS total score appeared balanced across the three treatment arms.

**Table 26. Study D1448C00006: Demographic and baseline disease characteristics (MITT sample)**

	Placebo N = 143	QTP 150 mg N = 143	QTP 300 mg N = 146	Total N = 432
<i>Age (yr) n</i>				
Mean (SD)	46.2 (10.9)	45.9 (11.0)	44.3 (11.3)	45.4 (11.1)
Median	48.0	47.0	46.0	47.0
Min – Max	20 – 65	20 – 64	19 – 64	19 – 65
<i>Sex – n (%)</i>				
Male	45 (31.5)	34 (23.8)	40 (27.4)	119 (27.5)
Female	98 (68.5)	109 (76.2)	106 (72.6)	313 (72.5)
<i>Race – n (%)</i>				
Black	14 (9.8)	10 (7.0)	11 (7.5)	35 (8.1)
Caucasian	128 (89.5)	128 (89.5)	133 (91.1)	389 (90.1)
Oriental	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Others	1 (0.7)	4 (2.8)	2 (1.4)	7 (1.6)
<i>Baseline MADRS- total score</i>				
Mean (SD)	27.6 (5.5)	27.2 (5.2)	27.6 (5.0)	27.5 (5.2)
Median	28.0	27.0	27.0	27.0
Min – Max	12 – 43	12 – 45	13 – 43	12 – 45

(Source: d1448c00006 Study Report; Tables 16 & 18, pages 97 & 99)

#### 3.1.5.4.2 Sponsor’s Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from randomization to Week 6 in the MADRS total score. The primary analysis model was a mixed effect ANCOVA model with baseline MADRS total score as a covariate, treatment as a fixed factor, and center as a random effect. Multiple hypotheses were tested sequentially. First the two primary hypotheses were tested using the Hommel procedure. If both primary hypotheses were significant, then the two secondary hypotheses were tested using the Hommel procedure. The primary analysis is summarized in Table 27. Quetiapine XR at 300 mg/day in combination with an antidepressant was statistically significantly superior to placebo in combination with an antidepressant. Quetiapine XR at 150 mg/day in combination with an antidepressant was not statistically significantly superior to placebo in combination with an antidepressant.

**Table 27. Study D1448C00006: Sponsor’s primary efficacy results: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg
Sample size	143	143	146
LS Means	-11.70	-13.60	-14.70
Difference from placebo (95% confidence interval)		-1.90 (-3.93, 0.14)	-2.99 (-5.02, -0.97)
Unadjusted p-values		0.067	0.004
Adjusted p-values		0.067	0.008

(Source: d1448c00006 Study Report; Table 21, page 106)

3.1.5.4.3 Sponsor's Efficacy Results for Key Secondary Endpoint

The key secondary efficacy variable was the change from randomization to Week 6 in the Q-LES-Q percent maximum total score. The key secondary analysis model was a mixed effect ANCOVA model with baseline Q-LES-Q percent maximum total score as a covariate, treatment as a fixed effect, and center as a random effect. Because only one dose of the primary hypotheses was rejected, the key secondary hypotheses were not tested. The results of the key secondary results presented in Table 28 are for descriptive purposes only.

**Table 28. Study D1448C00006: Sponsor's key secondary efficacy results: change from randomization to week 6 in the Q-LES-Q percent maximum total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg
Sample size	136	135	136
LS Means	11.32	10.37	11.82
Difference from placebo (95% confidence interval)		-0.96 (-4.59, 2.68)	0.50 (-3.15, 4.15)
Unadjusted p-values		0.606	0.789

(Source: d1448c00006 Study Report; Table 35, pages 121)

3.1.5.4.4 Sponsor's Other Efficacy Results

A primary sensitivity analysis: An analysis on the change from randomization to week 6 in the MADRS total score using a mixed model for repeated measures is summarized in Table 29. The model included treatment, visit, and treatment-by-visit interaction as fixed effects, center as random effect, and baseline MADRS total score as a covariate. Robust variance estimates for the fixed effects were used to test the treatment differences. The within subject variance was unstructured. Based on this sensitivity analysis, both doses of quetiapine were superior to placebo on the change from randomization to week 6 in the MADRS total score.

**Table 29. Study D1448C00006: Sponsor's primary sensitivity analysis: change from randomization to week 6 in the MADRS total score (OC) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg
Sample size	143	143	146
LS Means	-11.72	-14.28	-15.95
Difference from placebo (95% confidence interval)		-2.56 (-4.33, -0.80)	-4.24 (-6.07, -2.40)
Unadjusted p-values		0.005	<0.001

(Source: d1448c00006 Study Report; Table 11.2.1.4, page 329)

An analysis on the primary endpoint over time (LOCF): Table 30 summarizes an analysis of the change from randomization in the MADRS total score (LOCF) over time. The ANCOVA model similar to the primary analysis model was used. The response appeared consistent over time for the quetiapine XR 300 mg/day arm. In the 150 mg/day arm, greater responses appeared in Weeks 1 and 2 than in Weeks 4 and 6.

**Table 30. Study D1448C00006: Sponsor’s efficacy analysis: change from randomization in the MADRS total score (LOCF) over time in the MITT sample**

	Pbo	QTP 150mg	QTP 300mg	QTP 150mg – Pbo Diff	p-value*	QTP 300mg – Pbo Diff	p-value*
Week 1	-5.95	-9.06	-8.20	-3.10	<0.001	-2.25	0.002
Week 2	-9.05	-11.62	-11.46	-2.57	0.003	-2.40	0.005
Week 4	-11.51	-13.06	-13.72	-1.55	0.100	-2.21	0.019
Week 6	-11.70	-13.60	-14.70	-1.90	0.067	-2.99	0.004

(Source: d1448c00006 Study Report; Table 11.2.1.3.1, pages 322-324)

\*p-values are not adjusted for multiplicity

#### 3.1.5.4.5 Reviewer’s Results and Comments

This reviewer confirmed the findings on the primary and key secondary efficacy variables as presented in Table 27 and Table 28. Quetiapine XR at a 300 mg/day in combination with an antidepressant was superior to placebo in combination with an antidepressant on the change from randomization to week 6 in the MADRS total score.

Quetiapine XR at a 150 mg/day in combination with an antidepressant was not superior to placebo in combination with an antidepressant. Quetiapine XR was also not superior to placebo on the Q-LES-Q percent maximum score change from randomization to week 6.

### 3.1.6 Study D1448C00007

#### 3.1.6.1 Objectives

**Primary:** The primary objective of this study was to evaluate the efficacy of quetiapine XR 150 mg/day and 300 mg/day in combination with an antidepressant versus antidepressant in combination with placebo in patients with MDD, as assessed by the change from randomization to week 6 in the MADRS total score.

**Key Secondary:** The key secondary objective was to evaluate if quetiapine XR in combination with an antidepressant improves the health-related quality of life of patients with MDD, compared to an antidepressant in combination with placebo by assessing the change from randomization to week 6 in the Q-LES-Q percent maximum total score.

#### 3.1.6.2 Study Design

This was a 6-week, multicenter, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study. The study consisted of two periods. The first period was an enrollment period of up to 14 days. The second period was a six-week, double-blind, randomized phase. Patients who met all eligibility criteria were randomized to receive quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, or placebo in combination with the ongoing antidepressant treatment.

Male and female patients between the age of 18 and 65 years old were enrolled from May 2006 to April 2007. Patients were eligible to enroll if they were documented with a DSM-IV MDD, single episode or recurrent; had a HAM-D total score of at least 20 and HAM-D Item 1 score of at least 2 both at enrollment and at randomization; had a history during the current depressive episode of an inadequate response to 1 of the following antidepressants: amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine. Assessments of the primary endpoint, MADRS, were done on days 1, 8, 15, 29, and 43. Assessments of the key secondary endpoint, Q-LES-Q, were done on days 1, 29, and 43.

The sample size calculation was based on a 90% power and a 0.05 significant level. It was determined that 140 subjects per arm were needed to detect a 3.5-unit difference with a standard deviation of 9 for the change in the MADRS total score from randomization to week 6.

### *3.1.6.3 Efficacy Endpoints and Analyses*

Primary endpoint and analysis: The primary endpoint was the change from randomization to Week 6 in the MADRS total score. Missing values were imputed by the LOCF method. The primary efficacy variable was analyzed by a mixed model ANCOVA with MADRS total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

Key Secondary endpoint and analysis: The key secondary endpoint was the change in the Q-LES-Q percent maximum total score from randomization to Week 6. The short form of the Q-LES-Q consists of 16 items rated on a 5-point scale. Larger values indicate a higher perceived quality of life enjoyment and satisfaction. The Q-LES-Q total score is the sum of the first 14 items. This total score is converted to a percentage of the maximum score using the scoring conversion:

$$\text{Q-LES-Q percent maximum score} = \frac{\text{Q-LES-Q total score} - 14}{56} \times 100.$$

Missing values were imputed by the LOCF method. The key secondary endpoint was analyzed by a mixed model with Q-LES-Q percent maximum total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect.

A step-wise sequential testing procedure was used to handle multiple comparisons across the primary and secondary hypotheses. First, both primary hypotheses were tested. The Hommel procedure was used control the type I error rate between the two primary hypotheses. If both doses of quetiapine XR were statistically significantly superior to placebo, then the two secondary hypotheses would be tested. The Hommel procedure would also be used to control the type I error rate between the two secondary hypotheses.

### 3.1.6.4 Efficacy Results

#### 3.1.6.4.1 Study Population

Subjects were enrolled from 87 centers in Australia, Belgium, Canada, Czech, Finland, France, Germany, Norway, Poland, Romania, South Africa, and Sweden. A total of 572 subjects were screened and 493 subjects were randomized to 1 of the three treatment groups: placebo, quetiapine XR 150 mg/day, quetiapine XR 300 mg/day in combination with an antidepressant. The disposition of the subjects is summarized in Table 31. In Table 31 and all subsequent tables of this study, placebo, QTP 150 mg, QTP 300 mg are used to denote placebo, quetiapine XR 150 mg/day, quetiapine XR 300 mg/day in combination with an antidepressant.

Fourteen percent of the randomized subjects discontinued the study prematurely. The main reasons for the discontinuation were adverse events and patients not willing to continue. There were more adverse events in the quetiapine XR arms than in placebo. The discontinuation rate was highest for quetiapine XR 300 mg/day (18.4%), followed by the quetiapine XR 150 mg/day (12.6%), and then the placebo (11.0%).

**Table 31. Study D1448C00007: Disposition of patients**

	Placebo (N = 163)	QTP 150mg (N = 167)	QTP 300mg (N = 163)	Total (N = 493)
Randomized (not treated)	2	0	0	2
Randomized (treated)	161	167	163	491
<b>Discontinued study: n (%)</b>	<b>18 (11.0)</b>	<b>21 (12.6)</b>	<b>30 (18.4)</b>	<b>69 (14.0)</b>
-Lost to follow-up		3 (1.8)		3 (0.6)
-Adverse event	5 (3.1)	11 (6.6)	19 (11.7)	35 (7.1)
-Development of study specific discontinuation criteria			2 (1.2)	2 (0.4)
-Patients not willing to continue	5 (3.1)	7 (4.2)	3 (1.8)	15 (3.0)
-Lack of therapeutic response	5 (3.1)		1 (0.6)	6 (1.2)
-Eligibility criteria not fulfilled	1 (0.6)		2 (1.2)	3 (0.6)
-Severe non-compliance to protocol	1 (0.6)		3 (1.8)	4 (0.8)
-Other	1 (0.6)			1 (0.2)
<b>Completed 6-week randomized treatment period: n (%)</b>	<b>145 (89.0)</b>	<b>146 (87.4)</b>	<b>133 (81.6)</b>	<b>424 (86.0)</b>

(Source: d1448c00007 Study Report; Table 11.1.3.1, page 198)

The modified intent-to-treat (MITT) sample had 487 subjects. The demographics and baseline disease characteristics of the MITT sample are presented in Table 32. Patients in this study were between 18 and 65 years of age. The average age was 45 years old. The ratio of females to males was about 2 to 1. The majority of the subjects was Caucasian (98%). The distribution of the baseline MADRS total score appeared balanced across the three treatment arms.

**Table 32. Study D1448C00007: Demographic and baseline disease characteristics (MITT sample)**

	Placebo N = 160	QTP 150 mg N = 166	QTP 300 mg N = 161	Total N = 487
<i>Age (yr) n</i>				
Mean (SD)	44.8 (10.4)	46.0 (10.1)	45.5 (11.1)	45.4 (10.5)
Median	46.0	47.0	47.0	47.0
Min – Max	20 – 64	21 – 65	18 – 65	18 - 65
<i>Sex – n (%)</i>				
Male	56 (35.0)	51 (30.7)	51 (31.7)	158 (32.4)
Female	104 (65.0)	115 (69.3)	110 (68.3)	329 (67.6)
<i>Race – n (%)</i>				
Black	2 (1.3)	0 (0.0)	2 (1.2)	4 (0.8)
Caucasian	157 (98.1)	165 (99.4)	156 (96.9)	478 (98.2)
Oriental	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Others	0 (0.0)	1 (0.6)	2 (1.2)	3 (0.6)
<i>Baseline MADRS- total score</i>				
Mean (SD)	28.2 (5.6)	28.6 (5.4)	28.4 (5.5)	28.4 (5.5)
Median	28.0	29.0	29.0	28.0
Min – Max	7 – 42	14 – 44	14 – 44	7 – 44

(Source: d1448c00007 Study Report; Tables 16 & 17, pages 90 & 91)

#### 3.1.6.4.2 Sponsor’s Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from randomization to Week 6 in the MADRS total score. The primary analysis model was a mixed effect ANCOVA model with baseline MADRS total score as a covariate, treatment as a fixed factor, and center as a random effect. Multiple hypotheses were tested sequentially. First the two primary hypotheses were tested using the Hommel procedure. If both primary hypotheses were significant, then the two secondary hypotheses were tested using the Hommel procedure. The primary analysis is summarized in Table 33. Quetiapine XR at 150 mg/day and 300 mg/day in combination with an antidepressant were statistically significantly superior to placebo in combination with an antidepressant.

**Table 33. Study D1448C00007: Sponsor’s primary efficacy results: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg
Sample size	160	166	161
LS Means	-12.21	-15.26	-14.94
Difference from placebo (95% confidence interval)		-3.05 (-4.92, -1.17)	-2.73 (-4.62, -0.84)
Unadjusted p-values		0.002	0.005
Adjusted p-values		0.003	0.005

(Source: d1448c00007 Study Report; Table 20, pages 98-99)

*3.1.6.4.3 Sponsor's Efficacy Results for Key Secondary Endpoint*

The key secondary efficacy variable was the change from randomization to Week 6 in the Q-LES-Q percent maximum total score. The key secondary analysis model was a mixed effect ANCOVA model with baseline Q-LES-Q percent maximum total score as a covariate, treatment as a fixed effect, and center as a random effect. The key secondary analysis results are presented in Table 34. Both quetiapine XR in combination with an antidepressant groups did not separate from placebo in combination with an antidepressant.

**Table 34. Study D1448C00007: Sponsor's key secondary efficacy results: change from randomization to week 6 in the Q-LES-Q percent maximum total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg
Sample size	160	160	157
LS Means	12.58	14.70	12.81
Difference from placebo (95% confidence interval)		2.12 (-1.09, 5.33)	0.24 (-2.98, 3.46)
Unadjusted p-values		0.194	0.884
Adjusted p-values		0.389	0.884

(Source: d1448c00007 Study Report; Table 33, pages 113)

*3.1.6.4.4 Sponsor's Other Efficacy Results*

A primary sensitivity analysis: An analysis on the change from randomization to week 6 in the MADRS total score using a mixed model for repeated measures is summarized in Table 29. The model included treatment, visit, and treatment-by-visit interaction as fixed effects, center as random effect, and baseline MADRS total score as a covariate. Robust variance estimates for the fixed effects were used to test the treatment differences. The within subject variance was unstructured. This analysis corroborates with the primary efficacy analysis using an ANCOVA model on LOCF data.

**Table 35. Study D1448C00007: Sponsor's primary sensitivity analysis: change from randomization to week 6 in the MADRS total score (OC) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg
Sample size	160	166	161
LS Means	-12.51	-15.98	-16.16
Difference from placebo (95% confidence interval)		-3.47 (-5.55, -1.39)	-3.65 (-5.69, -1.62)
Unadjusted p-values		0.001	<0.001

(Source: d1448c00007 Study Report; Table 11.2.1.4, page 300)

An analysis on the primary endpoint over time (LOCF): Table 40 summarizes an analysis of the change from randomization in the MADRS total score (LOCF) over time. The ANCOVA model similar to the primary analysis model was used. The effects appeared consistent over time for both dose groups.

**Table 36. Study D1448C00007: Sponsor’s efficacy analysis: change from randomization in the MADRS total score (LOCF) over time in the MITT sample**

	Pbo	QTP 150mg	QTP 300mg	QTP 150mg – Pbo Diff	QTP 150mg – Pbo p-value*	QTP 300mg – Pbo Diff	QTP 300mg – Pbo p-value*
Week 1	-4.16	-6.52	-6.38	-2.36	<0.001	-2.22	<0.001
Week 2	-7.71	-10.03	-10.44	-2.32	0.002	-2.73	<0.001
Week 4	-10.77	-12.93	-12.97	-2.16	0.011	-2.20	0.010
Week 6	-12.21	-15.26	-14.94	-3.05	0.002	-2.73	0.005

(Source: d1448c00007 Study Report; Table 11.2.1.3.1, pages 293-295)

\*p-values are not adjusted for multiplicity

*3.1.6.4.5 Reviewer’s Results and Comments*

This reviewer confirmed the findings on the primary and key secondary efficacy variables as presented in Table 33 and Table 34. Quetiapine XR at 150 mg/day and 300 mg/day in combination with an antidepressant were superior to placebo in combination with an antidepressant based on the primary endpoint, change from randomization to week 6 in the MADRS total score, but not on the key secondary endpoint, the Q-LES-Q percent of maximum score.

**3.2 Evaluation of Safety**

The evaluation of safety was not performed and reported here. Please refer to the clinical review for the safety evaluation and report.

**4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

**4.1 Gender, Race and Age**

**4.1.1 Study D1448C00001**

*4.1.1.1 Gender*

The primary analysis stratified by gender is presented in Table 37. All three doses showed numerical improvements over placebo across males and females.

**Table 37. Study D1448C00001: Sponsor’s primary efficacy results by gender: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 50mg	QTP 150mg	QTP 300mg
<i>Females</i>				
Sample size	113	95	104	103
LS Means	-11.45	-13.90	-13.74	-15.21
Difference from placebo (95% confidence interval)		-2.45 (-5.22, 0.31)	-2.29 (-5.00, 0.41)	-3.76 (-6.46, -1.06)
<i>Males</i>				
Sample size	65	83	64	73
LS Means	-9.85	-12.50	-14.90	-11.87
Difference from placebo (95% confidence interval)		-2.65 (-5.75, 0.46)	-5.04 (-8.35, -1.74)	-2.02 (-5.22, 1.18)

(Source: d1448c00001 Study Report; Table 11.2.1.5.2, pages 333, 335)

#### 4.1.1.2 Race

Approximately 73% of the subjects were Caucasians and approximately 23% were black. To avoid small sample sizes in some subgroups, race is dichotomized to Caucasians versus others. The primary analysis stratified by race is presented in Table 38. The efficacy appeared consistent across the two race categories.

**Table 38. Study D1448C00001: Sponsor’s primary efficacy results by race: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 50mg	QTP 150mg	QTP 300mg
<i>Caucasians</i>				
Sample size	136	131	124	123
LS Means	-10.53	-12.94	-13.70	-13.64
Difference from placebo (95% confidence interval)		-2.41 (-4.82, -0.01)	-3.18 (-5.62, -0.74)	-3.11 (-5.55, -0.67)
<i>Others</i>				
Sample size	43	47	44	53
LS Means	-11.78	-14.14	-15.61	-14.30
Difference from placebo (95% confidence interval)		-2.35 (-6.42, 1.71)	-3.83 (-7.95, 0.29)	-2.51 (-6.46, 1.43)

(Source: d1448c00001 Study Report; Table 11.2.1.5.4, page 343 and reviewer’s results)

#### 4.1.1.3 Age

All subjects in this study were between 18 and 65 at entry. An analysis stratified by age is omitted from this review.

### 4.1.2 Study D1448C00002

#### 4.1.2.1 Gender

The primary analysis stratified by gender is presented in Table 39. For quetiapine XR, the treatment effect appeared higher for females than males.

**Table 39. Study D1448C00002: Sponsor’s primary efficacy results by gender: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg	DUL
<i>Females</i>				
Sample size	98	93	75	88
LS Means	-10.87	-15.04	-16.06	-13.99
Difference from placebo (95% confidence interval)		-4.17 (-6.90, -1.43)	-5.18 (-8.08, -2.29)	-3.12 (-5.89, -0.34)
<i>Males</i>				
Sample size	54	54	72	53
LS Means	-11.33	-13.49	-14.00	-14.90
Difference from placebo (95% confidence interval)		-2.16 (-5.77, 1.46)	-2.66 (-6.04, 0.71)	-3.57 (-7.21, 0.07)

(Source: d1448c00002 Study Report; Table 11.2.1.5.2, pages 342, 345)

4.1.2.2 Race

Approximately 74% of the subjects were Caucasians and approximately 21% were black. To avoid small sample sizes in some subgroups, race is dichotomized to Caucasians versus others. The primary analysis stratified by race is presented in Table 40. Caucasians patients appeared to have a larger treatment effect than non-Caucasians. This could be due to the larger placebo effect seen among non-Caucasian patients.

**Table 40. Study D1448C00002: Sponsor’s primary efficacy results by race: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg	DUL
<i>Caucasians</i>				
Sample size	105	111	110	107
LS Means	-9.53	-14.83	-14.80	-14.82
Difference from placebo (95% confidence interval)		-5.30 (-7.84, -2.76)	-5.27 (-7.82, -2.73)	-5.29 (-7.86, -2.73)
<i>Others</i>				
Sample size	47	36	37	34
LS Means	-14.27	-13.27	-15.81	-13.05
Difference from placebo (95% confidence interval)		1.00 (-3.23, 5.22)	-1.54 (-5.73, 2.65)	1.22 (-3.07, 5.51)

(Source: d1448c00002 Study Report; Table 11.2.1.5.4, page 352 and reviewer’s results)

4.1.2.3 Age

All subjects in this study were between 18 and 65 at entry. An analysis stratified by age is omitted from this review.

**4.1.3 Study D1448C00003**

4.1.3.1 Gender

The primary analysis stratified by gender is presented in Table 41. Consistent responses were seen both in males and females.

**Table 41. Study D1448C00003: Sponsor’s primary efficacy results by gender: change from randomization to week 8 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150/300 mg
<i>Females</i>		
Sample size	98	95
LS Means	-13.34	-16.80
Difference from placebo (95% confidence interval)		-3.46 (-6.18, -0.74)
<i>Males</i>		
Sample size	54	52
LS Means	-12.55	-16.06
Difference from placebo (95% confidence interval)		-3.51 (-6.71, -0.30)

(Source: d1448c00003 Study Report; Table 11.2.1.1.9, pages 289, 291)

#### 4.1.3.2 Race

Approximately 67% of the subjects were Caucasians and approximately 27% were black. To avoid small sample sizes in some subgroups, race is dichotomized to Caucasians versus others. The primary analysis stratified by race is presented in Table 42. The effect appeared smaller for Caucasian patients than for other patients.

**Table 42. Study D1448C00003: Sponsor's primary efficacy results by race: change from randomization to week 8 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150/300 mg
<i>Caucasians</i>		
Sample size	100	101
LS Means	-12.75	-15.51
Difference from placebo (95% confidence interval)		-2.76 (-5.37, -0.14)
<i>Others</i>		
Sample size	52	46
LS Means	-13.85	-18.59
Difference from placebo (95% confidence interval)		-4.74 (-8.14, -1.34)

(Source: d1448c00003 Study Report; Table 11.2.1.1.10, page 294 and reviewer's results)

#### 4.1.3.3 Age

All subjects in this study were between 18 and 64 at entry. An analysis stratified by age is omitted from this review.

### 4.1.4 Study D1448C00005

#### 4.1.4.1 Gender

The primary analysis stratified by gender is summarized below. The treatment effect appeared greater for males than for females.

**Table 43. Study D1448C00005: Sponsor’s primary efficacy analysis by gender: Time to depressed event (ITT sample). Wald’s test, comparison of QTP XR versus Placebo with Cox Regression**

	Placebo	QTP XR
<i>Females</i>		
Sample size	254	255
Numbers of relapses (%)	81 (31.9)	42 (16.5)
Comparison between treatment groups		
Hazard ratio		0.41
95% confidence interval		(0.29, 0.60)
<i>Males</i>		
Sample size	130	132
Numbers of relapses (%)	51 (39.2)	13 (9.8)
Comparison between treatment groups		
Hazard ratio		0.21
95% confidence interval		(0.11, 0.39)

(Source: Clinical Study Report: Study d1448C00005; Table 11.2.1.3, pages 591-592)

#### 4.1.4.2 Race

The majority of the subjects was Caucasians (88%) and black (9%). To avoid small sample sizes in some subgroups, race is dichotomized to Caucasians versus others. The primary analysis stratified by race is summarized below. Caucasians appeared to have a greater treatment effect than other patients.

**Table 44. Study D1448C00005: Sponsor’s primary efficacy analysis by race: Time to depressed event (ITT sample). Wald’s test, comparison of QTP XR versus Placebo with Cox Regression**

	Placebo	QTP XR
<i>Caucasians</i>		
Sample size	339	336
Numbers of relapses (%)	121 (35.7)	48 (14.3)
Comparison between treatment groups		
Hazard ratio		0.32
95% confidence interval		(0.23, 0.45)
<i>Others</i>		
Sample size	45	51
Numbers of relapses (%)	11 (24.4)	7 (13.7)
Comparison between treatment groups		
Hazard ratio		0.51
95% confidence interval		(0.20, 1.32)

(Source: Clinical Study Report: Study d1448C00005; Table 11.2.1.3, page 592 and reviewer’s results)

#### 4.1.4.3 Age

All subjects in this study were between 19 and 65 at entry. An analysis stratified by age is omitted from this review.

## 4.1.5 Study D1448C00006

### 4.1.5.1 Gender

The primary analysis stratified by gender is presented in Table 45. The effects appeared larger for male patients than for female patients.

**Table 45. Study D1448C00006: Sponsor's primary efficacy results by gender: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg
<i>Females</i>			
Sample size	98	109	106
LS Means	-12.18	-13.28	-14.72
Difference from placebo (95% confidence interval)		-1.10 (-3.58, 1.37)	-2.55 (-5.03, -0.06)
<i>Males</i>			
Sample size	45	34	40
LS Means	-11.67	-15.52	-15.51
Difference from placebo (95% confidence interval)		-3.86 (-7.79, 0.08)	-3.84 (-7.61, -0.07)

(Source: d1448c00006 Study Report; Table 11.2.1.5.2, pages 336-339)

### 4.1.5.2 Race

Approximately 90% of the subjects were Caucasians. To avoid small sample sizes in some subgroups, race is dichotomized to Caucasians versus others. The primary analysis stratified by race is presented in Table 46. Due to small sample sizes, it is difficult to assess the treatment effect for other races. For Caucasians, the treatment effects appeared consistent with the overall results.

**Table 46. Study D1448C00006: Sponsor's primary efficacy results by race: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg
<i>Caucasians</i>			
Sample size	128	128	133
LS Means	-12.14	-13.56	-14.85
Difference from placebo (95% confidence interval)		-1.42 (-3.63, 0.79)	-2.71 (-4.90, -0.53)
<i>Others</i>			
Sample size	15	15	13
LS Means	-10.58	-16.24	-16.05
Difference from placebo (95% confidence interval)		-5.66 (-11.90, 0.58)	-5.46 (-11.94, 1.01)

(Source: d1448c00006 Study Report; Table 11.2.1.5.4, page 346 and reviewer's results)

### 4.1.5.3 Age

All subjects in this study were between 19 and 65 at entry. An analysis stratified by age is omitted from this review.

## 4.1.6 Study D1448C00007

### 4.1.6.1 Gender

The primary analysis stratified by gender is presented in Table 47. The effects appeared consistent for both females and males.

**Table 47. Study D1448C00007: Sponsor's primary efficacy results by gender: change from randomization to week 6 in the MADRS total score (LOCF) in the MITT sample**

	Placebo	QTP 150mg	QTP 300mg
<i>Females</i>			
Sample size	104	115	110
LS Means	-12.67	-15.83	-15.40
Difference from placebo (95% confidence interval)		-3.16 (-5.48, -0.84)	-2.73 (-5.07, -0.38)
<i>Males</i>			
Sample size	56	51	51
LS Means	-11.38	-13.81	-13.96
Difference from placebo (95% confidence interval)		-2.43 (-5.89, 1.04)	-2.58 (-6.03, 0.88)

(Source: d1448c00007 Study Report; Table 11.2.1.5.2, pages 307 & 309)

### 4.1.6.2 Race

Approximately 98% of the subjects were Caucasians. An analysis stratified by race is omitted from this review.

### 4.1.6.3 Age

All subjects in this study were between 18 and 65 at entry. An analysis stratified by age is omitted from this review.

## 4.2 Other Subgroups

### 4.2.1 Study D1448C00005

#### 4.2.1.1 U.S.A. versus non-U.S.A.

The primary analysis stratified by U.S. versus non-U.S. is summarized below. The treatment effect appeared consistent in both strata.

**Table 48. Study D1448C00005: Sponsor’s primary efficacy analysis by region: Time to depressed event (ITT sample). Wald’s test, comparison of QTP XR versus Placebo with Cox Regression**

	Placebo	QTP XR
<i>U.S.A.</i>		
Sample size	250	252
Numbers of relapses (%)	94 (37.6)	38 (15.1)
Comparison between treatment groups		
Hazard ratio		0.32
95% confidence interval		(0.22, 0.47)
<i>Non-U.S.A.</i>		
Sample size	134	135
Numbers of relapses (%)	38 (28.4)	17 (12.6)
Comparison between treatment groups		
Hazard ratio		0.37
95% confidence interval		(0.21, 0.66)

(Source: Clinical Study Report: Study d1448C00005; Table 11.2.1.3, pages 593-594)

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

All six studies were positive on the primary efficacy variable on at least one dose under investigation. Among five studies that had the key secondary endpoint (Q-LES-Q percent maximum score), none of the studies was positive on the key secondary endpoint. The HAM-A was not a pre-specified endpoint, thus it cannot be used to support labeling claims.

Although the numerical evidence suggested that patients who took quetiapine XR benefited from the treatment early in the course of the trials, no appropriate statistical methods were pre-specified to assess this claim formally. Thus the claim that a significant improvement was observed within the first week and continuing throughout the study was not justified and could only be used descriptively.

### 5.2 Conclusions and Recommendations

The sponsor submitted seven efficacy and safety studies to seek claims for monotherapy, adjunctive therapy, and maintenance treatment for adult patients with major depressive disorder (MDD). Evidence of effectiveness for the monotherapy was demonstrated from three studies: D1448C00001, D1448C00002, and D1448C00003. Evidence of effectiveness for the adjunctive therapy to an antidepressant was demonstrated from two studies: D1448C00006 and D1448C00007. Evidence of effectiveness for maintenance therapy was demonstrated from one study: D1448C00005.

In studies D1448C00001, D1448C00002, D1448C00003, D1448C00006, and D1448C00007, the primary efficacy variable was the change from randomization to end visit (week 6 or week 8) in the Montgomery-Asberg Depression Rating (MADRS) total score. The Hamilton Rating Scale for Anxiety (HAM-A) was not a pre-specified endpoint, thus it can only serve as exploratory findings and do not support labeling claims. Furthermore, the claim that significant improvement was observed within the first week and continuing through the study was not justified because there were not appropriate statistical methods pre-specified.

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## **Clinical Pharmacology and Biopharmaceutics Review**

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NDA: 22-047 (S010, 011, 012)  
Drug: Quetiapine fumarate Extended Release Tablets  
Brand Name: Seroquel XR  
Indication: Treatment of Major Depressive Disorder  
Sponsor: AstraZeneca

Submission Type: Efficacy Supplement  
Submission Date: 2/27/08

Reviewer: Kofi A. Kumi, Ph.D.  
Team Leader: Raman Baweja, Ph.D.

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### **1. Executive Summary**

#### *1.1 Recommendations*

The Office of Clinical Pharmacology (OCP) has reviewed the data submitted to the Clinical Pharmacology and Biopharmaceutics sections of NDA 22-047 (S010, 011, 012) and finds the data acceptable. OCP proposes the following language to be included in the drug interaction section of the label

Antidepressants: Coadministration of bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine with quetiapine did not result in a consistent effect on the trough concentrations of the antidepressant drug. Large inter-patient variability was observed in the plasma trough concentrations of the antidepressants. Therefore, patients should be monitored closely when quetiapine is coadministered with antidepressant drugs.

#### *1.2. Phase IV Commitments recommended*

There are no Phase IV commitments

#### *1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings*

*Background:* Quetiapine extended-release (Seroquel XR) is marketed for the treatment of schizophrenia. The sponsor investigated the use of quetiapine XR as a treatment for major depressive disorder (MDD). This sNDA seeks approval of quetiapine XR for monotherapy, adjunct and maintenance treatment of MDD. The sNDA includes the results of 7 pivotal Phase III clinical studies designed to evaluate the safety and efficacy of Seroquel XR in the treatment of MDD. In the adjunctive treatment program, the sponsor evaluated the concentrations of co-administered antidepressant drugs to determine the effect of quetiapine on the antidepressant concentrations. The effect of the antidepressants on quetiapine concentrations was not determined. The review focuses on evaluating whether quetiapine has an effect on antidepressant concentrations.

*Coadministration of Quetiapine with Anti-depressants:* In the adjunctive studies, patients with MDD treated with quetiapine XR or placebo were included in the pharmacokinetic analysis to determine the effect of quetiapine on the steady state plasma concentration of the adjunct antidepressant. Permitted antidepressants for the study were amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine. There was a range in inter-patient antidepressant doses used in these studies, but the dose level for an individual patient

was maintained throughout the study. Patient antidepressant and metabolite plasma concentrations were assessed at randomization prior to receiving quetiapine XR and at Weeks 2 and 4. Patients were treated with placebo or with quetiapine XR at daily doses of either 150 or 300 mg. The following table contains the percent change at weeks 2 and 4 of treatment relative to baseline (randomization) concentrations of antidepressants.

*Results*

Mean Percent Change from Baseline (Randomization) of Antidepressant Concentrations to Weeks 2 and 4 of Treatment (Pooled Data)

Parameter	Visit	Treatment		
		Placebo	Quetiapine 150	Quetiapine 300
		Mean±SD % Change from Baseline		
Citalopram	Week 2	11.02 ± 49.83	25.90 ± 69.37	229.42 ± 709.70
	Week 4	3.92 ± 49.26	7.71 ± 76.73	198.00 ± 681.89
Duloxetine	Week 2	-2.63 ± 34.2	174.67 ± 564.63	33.54 ± 78.20
	Week 4	-2.72 ± 48.57	129.68 ± 257.03	27.12 ± 130.81
Escitalopram	Week 2	9.94 ± 72.37	-5.98 ± 22.25	6.78 ± 35.52
	Week 4	18.73 ± 111.28	19.68 ± 59.94	4.87 ± 39.24
Fluoxetine	Week 2	58.44 ± 105.35	29.12 ± 54.24	37.16 ± 108.08
	Week 4	62.77 ± 128.81	36.81 ± 83.20	72.42 ± 176.38
Norfluoxetine	Week 2	26.26 ± 42.07	57.86 ± 155.24	52.68 ± 176.69
	Week 4	37.00 ± 66.02	67.70 ± 202.52	75.55 ± 203.67
Paroxetine	Week 2	13.27 ± 44.72	73.26 ± 114.58	50.26 ± 62.81
	Week 4	31.85 ± 88.33	12.98 ± 40.56	43.26 ± 61.86
Sertraline	Week 2	29.37 ± 83.24	-2.91 ± 50.81	26.42 ± 79.85
	Week 4	289.17 ± 1256.6	-16.54 ± 26.56	7.52 ± 61.66
Desmethylsertraline	Week 2	37.35 ± 87.77	62.22 ± 204.22	25.57 ± 45.32
	Week 4	51.91 ± 100.78	10.11 ± 60.96	18.92 ± 54.46
Venlafaxine	Week 2	40.29 ± 74.30	0.41 ± 72.88	81.73 ± 322.01
	Week 4	-12.60 ± 32.12	0.78 ± 56.91	68.59 ± 391.33
O-desmethyl - venlafaxine	Week 2	21.58 ± 41.23	3.26 ± 42.74	19.00 ± 83.97
	Week 4	11.36 ± 46.13	8.37 ± 34.73	8.01 ± 106.73
Bupropion	Week 2	0.43 ± 27.29	16.25 ± 41.11	11.18 ± 21.17
	Week 4	48.29 ± 87.87	5.44 ± 15.36	0.29 ± 11.96

*Conclusions:* The effect of quetiapine on the antidepressant evaluated when they are co-administered together was not conclusive from this exploratory study. There was a great deal of variability in the plasma concentration data. Therefore, there was not consistent association

between the quetiapine XR dose being co-administered and the relative change observed from baseline (randomization). But evaluation of the individual data indicated that some patients had large increases in the concentration of their anti-depressant. It is recommended that caution should be exercised when quetiapine are co-administered with Citalopram, Duloxetine, Escitalopram, Fluoxetine, Paroxetine, Setraline, Venlafaxine and Bupropion. The effect of antidepressants on quetiapine was not evaluated in this study. Only one patient was on amitriptyline, therefore it was not included in the analysis. The sponsor conducted a literature review to collect information on the potential CYP enzyme inhibition and induction of the most commonly prescribed antidepressants. Overall, the evidence indicates a low potential for significant clinical drug interactions that would arise from either inhibition or induction of human cytochrome P450 enzymes involved in the metabolism of quetiapine or antidepressants. The reviewer agrees with the conclusions of the literature review

## **2. Question Based Review**

The QBR section of the review has used a deductive approach (i.e. starts with conclusions followed with supportive details) as instructed by CDER Review Template MaPP 4000.4.

### *2.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology?*

Quetiapine was first approved as an immediate-release (IR) formulation in 1997 for the treatment of schizophrenia. Quetiapine IR pharmacokinetics have been described in the original application (NDA 20-639) for the treatment of schizophrenia, acute mania in bipolar disorder and for depressive episodes in bipolar disorder. Quetiapine pharmacokinetics and biopharmaceutics after administration of quetiapine XR were described in the application for treatment of schizophrenia (NDA 22-047). The Pharmacokinetics and Biopharmaceutics information for quetiapine in these applications have been cross-reference in the current submission for MDD. The Clinical pharmacology information in this application focuses on the effect of quetiapine on antidepressant therapy when they are co-administered together in adjunctive therapy.

### *2.2 General Clinical Pharmacology and Biopharmaceutics*

#### *2.2.1 What is the proposed therapeutic indication for quetiapine XR in this submission?*

This sNDA seeks approval of quetiapine XR for monotherapy, adjunct and maintenance treatment of MDD.

#### *2.2.2 What are the proposed dosage for MDD and route of administration?*

Initial dosing should begin at 50 mg on Days 1 and 2, and be increased to 150 mg on Days 3 and 4. On Day 5 and onwards, if necessary, adjustments can be made upwards or downwards within the dose range (b) (4) to 300 mg depending upon the clinical response and tolerance of the patient. Quetiapine XR should be administered once daily, preferably in the evening. Quetiapine XR is intended to be administered orally. Quetiapine XR tablets should be swallowed whole and not split, chewed or crushed.

*2.2.3 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

The sponsor reported that the efficacy of quetiapine XR in the treatment of MDD after 6 or 8 weeks of monotherapy or adjunct treatment was demonstrated in doses of 50 to 300 mg daily. The sponsor reported that the most consistent evidence for efficacy was noted for the 150 and 300 mg daily doses. The sponsor reported that clinically relevant relief of depressive symptoms was seen as early as Day 4 of treatment for doses of 50 to 300 mg daily.

The application included 6 acute treatment studies (Studies 1, 2, 3, 4, 6, and 7) and 1 maintenance treatment study (Study 5) to evaluate the efficacy and safety of quetiapine XR in the treatment of MDD. Studies 1, 2, 3, and 4 were monotherapy treatment studies conducted in patients with MDD, whereas Studies 6 and 7 used quetiapine XR as an adjunct to on-going antidepressant therapy in patients with MDD who had had an inadequate response to antidepressant monotherapy. Studies 1, 2, 6, and 7 used fixed doses of quetiapine XR of 150 mg/day and 300 mg/day (Study 1 included a 50 mg/day treatment group), while Studies 3 and 4 used modified fixed doses of 150 mg/day and 300 mg/day; patients were initially randomized to quetiapine 150 mg/day; after 2 weeks of treatment, patients who had an inadequate response [failure to decrease MADRS score by at least 20%] received a doubling of their initial dose. Positive controls were utilized in Study 2 (duloxetine 60 mg daily) and Study 4 (escitalopram 10 or 20 mg daily) for assay sensitivity. Prior to randomization, there was a period of up to 28 days (up to 14 days for Studies 6 and 7) for washout of all psychotropic medications (except antidepressants in Studies 6 and 7) to ensure that patients were stable and continued to have adequate depressive symptoms requiring treatment. After randomization, the efficacy of the study treatments on symptoms of MDD was assessed at weekly intervals through Week 6 (Studies 1, 2, 6, and 7) or Week 8 (Studies 3 and 4). All studies except Study 7 included a 2-week post-treatment follow-up period, with a 1-week down-titration period in Studies 2 and 4. Down-titration of dose occurred only with quetiapine XR 300 mg/day and active comparator. The clinical program also included a maintenance treatment study (Study 5) to evaluate the effects of quetiapine XR in preventing the relapse of depressive episodes in patients with MDD who were stable for at least 12 weeks on quetiapine XR. The study consisted of 4 periods: enrollment (up to 28 days), open-label run-in (4 to 8 weeks), open-label stabilization (at least 12 weeks) and double-blind (treatment with quetiapine XR or placebo) randomized treatment period (up to 52 weeks). The quetiapine XR dose was flexible (50 mg/day, 150 mg/day, or 300 mg/day). Refer to medical review for Agency's conclusions of safety and efficacy of quetiapine XR in MDD.

In Studies 6 and 7, sites were instructed to take trough or pre-dose plasma concentration samples at randomization (baseline) and at Weeks 2 and 4. If due to scheduling difficulties at the study sites, a pre-dose sample was not possible, the sites were instructed to take the PK sample at the same time following dosing at each visit.

*2.2.4 Is there a potential for pharmacokinetic interaction between quetiapine or its metabolites with various antidepressants and their metabolites?*

Pooled analysis from two studies (studies 6 and 7) showed that trough concentrations of antidepressants evaluated and their metabolites were highly variable. Due to the large variability observed, caution should be used when these drugs are co-administered together. The effect of the antidepressants on quetiapine concentrations was not evaluated in these studies.

The sponsor conducted a multicenter, double-blind, randomized, parallel-group, placebo controlled phase III study of the efficacy and safety of quetiapine fumarate extended-release in combination with an antidepressant in the treatment of patients with major depressive disorder with inadequate response to an antidepressant treatment. One of the secondary objectives of these studies was to evaluate if quetiapine XR in combination with an antidepressant changes the plasma level of antidepressant by assessing the change from randomization to Week 2 and Week 4 in plasma concentration of antidepressant. The study evaluated quetiapine XR 150 mg/day and 300 mg/day in combination with an antidepressant in the treatment of patients with MDD who have shown an inadequate response to antidepressant monotherapy. Patients continued to maintain the same antidepressant therapy from the period beginning at enrollment through the end of double-blind treatment. Patients should have been on treatment with 1 of the following antidepressants for at least 6 weeks prior to enrollment (at least minimum effective antidepressant dose according to the prescribing information, with at least 1 dose increase when permitted according to the prescribing information: amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine. The mean change of the individual changes in plasma concentrations at Weeks 2 and 4 relative to the baseline concentration was calculated for each antidepressant and metabolite of interest. The following table contains mean values of antidepressant and metabolite plasma concentrations and change from randomization to Weeks 2 and 4. Amitriptyline is not included in the table since there was values for only 1 patient.



Antidepressant and metabolite plasma concentrations and change from randomization to Weeks 2 and 4 (Pooled Data) contd.

Parameter (ng/mL)	Visit	Placebo	QTR XR 150 mg	QTR XR 300 mg
Paroxetine		n = 16	n = 9	n = 9
		Mean ± SD		
		Placebo	QTR XR 150 mg	QTR XR 300 mg
	Randomization	83.63 ± 92.24	110.36 ± 68.19	77.81 ± 87.91
	Wk 2	84.14 ± 99.28	134.04 ± 77.44	94.38 ± 66.05
	Wk 2 % change	13.27 ± 44.27	73.26 ± 114.58	50.26 ± 62.81
	Wk 4	92.12 ± 88.65	106.96 ± 59.53	139.43 ± 193.69
	Wk 4 % change	31.85 ± 88.33	12.98 ± 40.56	43.26 ± 61.86
Sertraline		n = 31	n = 25	n = 30
		Mean ± SD		
	Randomization	44.94 ± 34.83	50.19 ± 30.68	38.71 ± 27.66
	Wk 2	47.13 ± 30.38	42.91 ± 30.48	36.99 ± 29.88
	Wk 2 % change	29.38 ± 83.24	-2.91 ± 50.81	26.42 ± 79.85
	Wk 4	45.74 ± 26.79	41.70 ± 30.68	38.78 ± 29.24
	Wk 4 % change	289.17 ± 1256.71	-16.54 ± 26.56	7.52 ± 61.66
Desmethylsertraline		n = 31	n = 26	n = 30
		Mean ± SD		
	Randomization	73.46 ± 40.72	80.88 ± 51.10	66.91 ± 57.77
	Wk 2	87.79 ± 45.57	81.98 ± 52.17	66.78 ± 55.90
	Wk 2% change	37.35 ± 87.77	62.22 ± 204.22	25.57 ± 45.45
	Wk 4	82.11 ± 44.20	80.14 ± 52.72	75.24 ± 52.58
	Wk 4 % change	51.91 ± 100.78	10.11 ± 60.96	18.92 ± 54.46
Venlafaxine		n = 27	n = 29	n = 28
		Mean ± SD		
	Randomization	144.61 ± 192.91	95.54 ± 74.30	109.47 ± 107.13
	Wk 2	187.52 ± 257.86	68.57 ± 47.58	83.54 ± 81.04
	Wk 2% change	40.29 ± 74.30	0.41 ± 72.88	81.73 ± 322.0
	Wk 4	157.71 ± 196.47	73.81 ± 52.95	83.80 ± 97.99
	Wk 4 % change	-12.60 ± 32.12	0.78 ± 56.91	68.59 ± 391.13
O-Desmethyl-venlafaxine		n = 27	n = 29	n = 28
		Mean ± SD		
	Randomization	220.19 ± 121.63	234.44 ± 143.47	203.29 ± 129.39
	Wk 2	241.42 ± 124.06	225.91 ± 174.60	189.00 ± 111.43
	Wk 2% change	21.58 ± 41.23	3.26 ± 42.74	19.00 ± 83.97
	Wk 4	254.16 ± 176.70	226.04 ± 153.41	189.50 ± 146.63
	Wk 4 % change	11.36 ± 46.13	8.37 ± 34.73	8.01 ± 106.73

Antidepressant and metabolite plasma concentrations and change from randomization to Weeks 2 and 4 (Pooled Data) contd.

Parameter (ng/mL)	Visit	Placebo	QTR XR 150 mg	QTR XR 300 mg
Bupropion		n = 10	n = 18	n = 13
		Mean ± SD		
	Randomization	113.70 ± 77.22	58.69 ± 38.51	45.52 ± 47.97
	Wk 2	101.88 ± 79.39	63.27 ± 47.82	56.34 ± 59.42
	Wk 2 % change	0.43 ± 27.29	16.25 ± 41.11	11.18 ± 21.17
	Wk 4	155.84 ± 127.71	69.56 ± 34.03	49.80 ± 59.59
	Wk 4 % change	48.29 ± 87.87	5.44 ± 15.36	0.29 ± 11.96

Due to the high variability in the data, definite conclusions cannot be drawn from this data. Sources of variability probably included time of antidepressant administration, missed doses, and mismatches between groups in dosing amounts for a given antidepressant. Literature review by the sponsor revealed little propensity for significant interaction via known metabolic pathways. It is recommended that patients be observed closely when these anti-depressants are administered and doses of anti-depressants adjusted accordingly.

*2.2.4 What were the sponsor's overall safety conclusions for the adjunctive therapy?*

The sponsor reported that overall, quetiapine XR treatment in a dose range from 50 mg to 300 mg once daily was generally safe and well-tolerated for the treatment of patients with MDD and consistent with the known safety profile of quetiapine. The sponsor reported that in the acute adjunct therapy, a higher incidence of adverse events was seen for quetiapine XR-treated patients compared to placebo-treated patients. The most common adverse events associated with quetiapine XR treatment were dry mouth, sedation, somnolence, and dizziness. The incidence of syncope was low and similar in all treatment groups. Most adverse events were mild to moderate in intensity. The incidence of AEs were similar irrespective of age, race, sex, or region and showed no consistent relationship to dose group.

*2.2.5 What were the analytical method used to determine the plasma concentration of the antidepressants and their metabolites?*

A validated liquid chromatography with a tandem mass spectrometry (LC/MS/MS) was used to determine the concentration of the anti-depressants and their metabolites. The analytical methods used are acceptable.

Fluoxetine and norfluoxetine were extracted using a liquid-liquid extraction procedure. The remaining analytes were extracted from human plasma using a solid phase extraction procedure. The extracts underwent liquid chromatography (LC) and the analytes were detected using tandem mass spectrometry (MS/MS) detection. The analytical method was considered to be precise and accurate provided the inter-assay precision (%CV) and accuracy (%RE) were ≤15% and within ±15%, respectively, with the exception of the LLOQ where ≤20% (%CV) and within ±20% (%RE) were accepted. The in process controls set by the sponsor were met during the analysis of the samples and are acceptable.

### **3. Detailed Labeling Recommendations**

Detailed OCP Labeling Recommendations are incorporated in the Proposed Label attached under Appendices

### **4. Appendix**

Proposed Label with OCP recommendations. OCP edits are noted as “Track Changes” in the proposed label

Clinical Pharmacology and Biopharmaceutics Individual Reports

**55 Pages Immediately Following Withheld - b(4) Draft Labeling**

**Title (Protocol D1448C00006):** A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo controlled Phase III Study Of The Efficacy And Safety Of Quetiapine Fumarate Extended-Release (SEROQUEL XR™) In Combination With An Antidepressant In The Treatment Of Patients With Major Depressive Disorder With Inadequate Response To An Antidepressant Treatment (Pearl Study)

Introduction: The review focuses on secondary objective 8 (below) to determine whether co-administration of quetiapine with antidepressant alters the plasma concentrations of the antidepressant.

Objectives: The primary objective of the study was to evaluate the efficacy of quetiapine fumarate extended-release in combination with an antidepressant versus an antidepressant in combination with placebo in patients with Major Depressive Disorder (MDD) who have had an inadequate response to antidepressant monotherapy.

The secondary objectives were:

1. To evaluate if quetiapine XR in combination with an antidepressant improves health related quality of life of patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;
2. To evaluate if quetiapine XR in combination with an antidepressant reduces anxiety symptoms in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;
3. To evaluate if quetiapine XR in combination with an antidepressant improves sleep quality in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;
4. To evaluate if quetiapine XR in combination with an antidepressant is effective in reducing suicidal ideation in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;
5. To evaluate if quetiapine XR in combination with an antidepressant improves somatic symptoms in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;
6. To evaluate if quetiapine XR in combination with an antidepressant improves satisfaction with medication in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;
7. To evaluate if quetiapine XR in combination with an antidepressant is as safe and well tolerated as an antidepressant in combination with placebo in the treatment of patients with MDD who have had an inadequate response to antidepressant monotherapy;
8. To evaluate if quetiapine XR in combination with an antidepressant changes the plasma level of antidepressant by assessing the change from randomization to Week 2 and Week 4 in plasma concentration of antidepressant.

Study Design: This was an 8-week, multicenter, double-blind, randomized, parallel-group, placebo controlled, double-dummy, Phase III study of the efficacy and safety of quetiapine XR 150 mg/day and 300 mg/day in combination with an antidepressant in the treatment of patients with MDD who have shown an inadequate response to antidepressant monotherapy. The study comprised 3 periods: an enrollment and washout period of up to 14 days (for the discontinuation of all prohibited medications), a 6-week randomized treatment period, and a 2-week follow-up period. Patients continued to maintain the same antidepressant therapy from the period beginning at enrollment through the end of double-blind treatment.

Patients should have been on treatment with 1 of the following antidepressants for at least 6 weeks prior to enrollment (at least minimum effective antidepressant dose according to the prescribing information), with at least 1 dose increase when permitted according to the prescribing information:

- amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine.

In addition, patients had to have a Hamilton Rating Scale for Depression (HAM-D) (17 item, hereafter referred to as HAM-D) total score  $\geq 20$  and a HAM-D Item 1 (depressed mood, hereafter referred to as HAM-D Item 1) score  $\geq 2$  at both enrollment and randomization.

Eligible patients underwent a washout period of up to 14 days for the discontinuation of all prohibited medications. Patients then entered a 6-week treatment period, when they were randomly assigned to blinded treatment in a 1:1:1 ratio to 150 mg/day quetiapine XR, 300 mg/day quetiapine XR, or placebo (each in combination with the ongoing antidepressant treatment). All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. Patients in the quetiapine XR 150-mg/day group maintained this dose through the end of the randomized treatment period. Patients in the quetiapine XR 300-mg/day group were up-titrated to 300 mg/day on Day 5, and then maintained this dose through the end of the randomized treatment period. The ongoing treatment with the antidepressant was maintained at the same dose throughout the study. During the 2-week follow-up period, no down-titration of quetiapine XR was performed since the dose of antidepressant was maintained. Study treatment was given in tablets of the following doses (batch number): quetiapine XR 50 mg (LJ4701, LJ4706), quetiapine XR 300 mg (9049K, 9051K), placebo 50-mg match (CL879X), and placebo 300-mg match (CE891X).

Study sites were instructed to take trough or pre-dose plasma concentration samples at randomization (baseline) and at Weeks 2 and 4. If due to scheduling difficulties at the study sites, a pre-dose sample was not possible, the sites were instructed to take the PK sample at the same time following dosing at each visit. Tubes were labeled with subject identification information, the antidepressant being administered, and the time and date of the sample. All samples were taken using aseptic technique. Dose date and time information for the PK sample of interest and 2 preceding doses were collected to assess whether patients were compliant with their therapy when the PK sample was taken.

Analytical Method: Samples for measurement of drug and metabolite concentrations were analyzed using fully validated bioanalytical methods. Fluoxetine and norfluoxetine were extracted using a liquid-liquid extraction procedure. The remaining analytes were extracted from human plasma using a solid phase extraction procedure. The extracts underwent liquid chromatography (LC) and the analytes were detected using tandem mass spectrometry (MS/MS) detection. The following table provides the calibration ranges in human plasma.

Study Number D1448C00006. Summary of calibration ranges in human plasma

Analyte	LLOQ (ng/mL)	ULQ (ng/mL)
Amitriptyline	1.00	250
Nortriptyline	1.00	250
Bupropion	TBD	TBD
Hydroxybupropion	TBD	TBD
Erythrohydrobupropion	TBD	TBD
Threohydrobupropion	TBD	TBD
Citalopram	0.500	250
Duloxetine	1.00	250
Fluoxetine	1.00	500
Norfluoxetine	1.00	500
Escitalopram	0.500	250
Paroxetine	1.00	250
Sertraline	1.00	250
Desmethylsertraline	1.00	250
Venlafaxine	1.00	250
O-Desmethylvenlafaxine	1.00	250

TBD To be determined.

Precision and Accuracy Summary Table for Calibration Standards

Analyte	%CV Value		%RE Value	
	Minimum	Maximum	Minimum	Maximum
Amitriptyline	1.4	5.3	-1.8	2.0
Nortriptyline	0.9	3.6	-5.0	4.0
Bupropion	TBD	TBD	TBD	TBD
Hydroxybupropion	TBD	TBD	TBD	TBD
Erythrohydrobupropion	TBD	TBD	TBD	TBD
Threohydrobupropion	TBD	TBD	TBD	TBD
Citalopram	1.5	4.6	-2.8	1.6
Duloxetine	2.7	6.9	-5.6	4.0
Escitalopram	1.6	6.1	-3.6	2.3
Fluoxetine	3.7	8.7	-4.4	3.2
Norfluoxetine	2.6	8.8	-3.2	4.5
Paroxetine	3.1	7.6	-1.6	1.6
Sertraline	3.2	7.6	-2.3	2.5
Desmethylsertraline	3.6	7.1	-2.0	3.5
Venlafaxine	1.4	4.9	-2.4	1.7
O-Desmethylvenlafaxine	1.9	8.3	-1.5	3.2

TBD To be determined

Precision and Accuracy Summary Table for QC Samples

Analyte	%CV Value		%RE Value	
	Minimum	Maximum	Minimum	Maximum
Amitriptyline	5.8	12.7	-5.0	4.0
Nortriptyline	4.8	6.5	-2.2	9.3
Bupropion	TBD	TBD	TBD	TBD
Hydroxybupropion	TBD	TBD	TBD	TBD
Erythrohydrobupropion	TBD	TBD	TBD	TBD
Threohydrobupropion	TBD	TBD	TBD	TBD
Citalopram	5.2	11.9	0.6	6.0
Duloxetine	2.6	3.7	-7.2	-3.2
Escitalopram	3.7	5.9	-1.1	0.0
Fluoxetine	5.6	8.5	-4.6	3.0
Norfluoxetine	3.8	7.2	-4.6	3.7
Paroxetine	2.7	5.2	0.6	7.0
Sertraline	6.0	8.1	-3.9	3.0
Desmethylsertraline	6.6	8.3	-7.2	3.3
Venlafaxine	2.8	6.0	-1.7	-1.0
O-Desmethylvenlafaxine	3.7	5.5	-3.6	-3.0

TBD To be determined.

Human plasma samples from AstraZeneca Study D1448C00006 were analyzed successfully for the 8 of the 9 antidepressant drugs and their respective metabolites. The repeat analyses of samples fell into 5 categories: Repeated by Error (RBE), Processing Error (PE), Over the Calibration Curve (OCC), Poor Chromatography (PC) and Questionable Value (QV). Samples were recorded as QV because their initial results were OCC and the re-assay results were either BLQ or at the lower range of calibration curve. To confirm the results, the QV samples were re-assayed in duplicate with dilution.

Bupropion was extracted from human plasma using a solid phase extraction procedure. The extracts underwent liquid chromatography (LC) and the analyte was detected using tandem mass spectrometry (MS/MS) detection. The Bupropion calibration in human plasma range from 10 to 2000 ng/mL. The minimum and maximum values for Bupropion precision (%CV) for calibration standards were 3.4 and 7.8, respectively. The minimum and maximum values of accuracy (%RE) for calibration standards were -2.6 and 3.4, respectively. The minimum and maximum precision (%CV) values for Bupropion QC samples were 3.9 and 7.4, respectively. The minimum and maximum accuracy (%RE) values for Bupropion QC samples were -6.0 and -0.3, respectively.

The analytical methods were acceptable. However, the sponsor did not provide the analytical method and quality control parameters for bupropion metabolites.

Pharmacokinetic Data Analysis: Change from randomization to Week 2 and Week 4 in the plasma concentration of antidepressant.

Pharmacokinetic Results: The following tables provided the mean plasma concentrations and change from the concentrations observed at randomization to weeks 2 and 4.

Plasma concentration levels and change from randomization to Weeks 2 and 4

Antidepressant			PLA N=75	QTP150 N=72	QTP300 N=68
Bupropion	N <sup>a</sup>		10	17	10
	Randomization	Mean (SD)	113.7 (77.2)	61.2 (38.0)	55.3 (50.6)
	Week 2	Mean (SD)	101.9 (79.4)	63.3 (47.8)	64.4 (63.0)
	Change	Mean (SD)	-7.1 (20.6)	-0.4 (17.5)	6.9 (15.2)
	% Change	Mean (SD)	0.4 (27.3)	16.2 (41.1)	13.2 (22.1)
		Median (range)	-12.3 (-23 to 47)	11.2 (-32 to 87)	19.9 (-28 to 38)
	Week 4	Mean (SD)	155.8 (127.7)	74.1 (31.2)	65.3 (65.8)
	Change	Mean (SD)	11.0 (15.4)	1.8 (11.6)	2.2 (11.0)
	% Change	Mean (SD)	48.3 (87.9)	5.1 (16.0)	-1.6 (13.0)
		Median (range)	10.3 (-7 to 179)	8.7 (-24 to 26)	0.0 (-20 to 15)
Citalopram	N <sup>a</sup>		6	3	4
	Randomization	Mean (SD)	70.2 (35.8)	39.0 (25.1)	98.5 (77.5)
	Week 2	Mean (SD)	87.6 (36.7)	44.4 (27.9)	130.1 (52.2)
	Change	Mean (SD)	11.9 (39.6)	11.0 (4.9)	31.6 (47.9)
	% Change	Mean (SD)	31.1 (83.8)	77.7 (91.2)	673.6 (1334.2)
		Median (range)	3.6 (-20 to 179)	77.7 (13 to 142)	11.4 (-3 to 2675)
	Week 4	Mean (SD)	68.4 (34.2)	38.6 (53.4)	130.5 (55.7)
	Change	Mean (SD)	-0.9 (9.0)	-14.8 (48.9)	32.0 (50.6)
	% Change	Mean (SD)	1.7 (14.5)	-31.8 (94.2)	662.3 (1307.0)
		Median (range)	0.5 (-12 to 18)	-31.8 (-98 to 35)	22.2 (-18 to 2623)

Plasma concentration levels and change from randomization to Weeks 2 and 4

<b>Antidepressant</b>			<b>PLA</b> N=75	<b>QTP150</b> N=72	<b>QTP300</b> N=68
Duloxetine	N <sup>a</sup>		7	10	9
	Randomization	Mean (SD)	39.5 (18.4)	43.2 (38.3)	50.4 (40.4)
	Week 2	Mean (SD)	31.3 (14.8)	53.8 (60.5)	72.7 (35.7)
	Change	Mean (SD)	-4.8 (9.6)	14.7 (49.4)	15.9 (29.7)
	% Change	Mean (SD)	-4.2 (25.5)	229.8 (694.5)	73.1 (78.5)
		Median (range)	-8.6 (-29 to 34)	-16.7 (-72 to 1945)	61.5 (-30 to 171)
	Week 4	Mean (SD)	43.7 (28.0)	42.3 (34.0)	61.5 (48.7)
	Change	Mean (SD)	0.7 (24.1)	5.0 (27.7)	17.4 (49.9)
	% Change	Mean (SD)	1.9 (48.8)	185.7 (319.6)	86.4 (167.2)
		Median (range)	-9.2 (-60 to 72)	10.1 (-42 to 653)	60.6 (-57 to 423)
Escitalopram	N <sup>a</sup>		12	10	5
	Randomization	Mean (SD)	41.9 (27.9)	40.6 (28.9)	50.4 (28.7)
	Week 2	Mean (SD)	39.2 (36.7)	35.6 (30.9)	44.9 (23.1)
	Change	Mean (SD)	2.5 (11.0)	-5.1 (10.4)	4.0 (24.2)
	% Change	Mean (SD)	-4.6 (39.4)	-15.4 (26.7)	21.5 (45.1)
		Median (range)	0.7 (-96 to 35)	-2.9 (-57 to 18)	36.6 (-44 to 57)
	Week 4	Mean (SD)	48.0 (35.0)	28.2 (19.5)	47.0 (18.4)
	Change	Mean (SD)	6.7 (14.3)	-5.9 (12.9)	-6.6 (26.0)
	% Change	Mean (SD)	56.7 (160.3)	-17.1 (29.5)	9.7 (51.5)
		Median (range)	8.2 (-30 to 525)	-10.7 (-57 to 18)	9.8 (-44 to 63)

Plasma concentration levels and change from randomization to Weeks 2 and 4

Antidepressant			PLA N=75	QTP150 N=72	QTP300 N=68
Fluoxetine	N <sup>a</sup>		10	10	9
	Randomization	Mean (SD)	152.4 (125.4)	229.7 (163.1)	166.4 (145.2)
	Week 2	Mean (SD)	230.7 (138.6)	285.8 (151.5)	207.3 (171.1)
	Change	Mean (SD)	51.3 (88.6)	24.7 (55.4)	24.0 (26.0)
	% Change	Mean (SD)	68.6 (131.9)	15.9 (21.1)	17.6 (13.4)
		Median (range)	35.8 (-34 to 382)	15.8 (-14 to 54)	22.3 (-3 to 34)
	Week 4	Mean (SD)	209.4 (142.2)	233.7 (118.5)	166.9 (114.1)
	Change	Mean (SD)	42.5 (81.0)	9.7 (65.5)	20.7 (51.8)
	% Change	Mean (SD)	58.9 (131.5)	14.4 (18.5)	47.5 (100.3)
		Median (range)	10.7 (-29 to 393)	17.8 (-24 to 35)	6.8 (-12 to 287)
Norfluoxetine	N <sup>a</sup>		10	10	9
	Randomization	Mean (SD)	119.8 (63.6)	167.9 (86.7)	120.5 (72.7)
	Week 2	Mean (SD)	151.5 (49.4)	207.3 (85.8)	130.3 (51.1)
	Change	Mean (SD)	15.5 (32.4)	18.9 (31.8)	9.5 (17.0)
	% Change	Mean (SD)	18.6 (32.9)	13.6 (20.0)	10.5 (15.1)
		Median (range)	8.9 (-15 to 93)	11.0 (-3 to 60)	14.0 (-7 to 31)
	Week 4	Mean (SD)	146.1 (53.4)	179.4 (74.5)	126.6 (65.6)
	Change	Mean (SD)	26.4 (32.2)	9.9 (40.1)	9.8 (26.6)
	% Change	Mean (SD)	45.3 (72.9)	11.6 (19.1)	41.5 (88.9)
		Median (range)	12.8 (-7 to 220)	11.4 (-23 to 45)	16.0 (-17 to 254)

Plasma concentration levels and change from randomization to Weeks 2 and 4

Antidepressant			PLA N=75	QTP150 N=72	QTP300 N=68
Paroxetine	N <sup>a</sup>		5	3	5
	Randomization	Mean (SD)	38.6 (24.2)	109.1 (40.9)	61.5 (65.6)
	Week 2	Mean (SD)	51.2 (35.3)	129.4 (61.7)	90.4 (82.9)
	Change	Mean (SD)	9.3 (14.4)	43.8 (55.6)	20.3 (25.0)
	% Change	Mean (SD)	20.4 (43.8)	49.0 (61.4)	36.1 (39.9)
		Median (range)	19.3 (-32 to 75)	49.0 (6 to 92)	24.7 (3 to 92)
	Week 4	Mean (SD)	55.5 (39.2)	145.0 (62.5)	33.1 (NA)
	Change	Mean (SD)	16.8 (39.6)	35.9 (24.7)	-5.0 (NA)
	% Change	Mean (SD)	64.1 (144.7)	31.4 (18.6)	-13.1 (NA)
		Median (range)	33.9 (-64 to 311)	36.5 (11 to 47)	-13.1 (-13 to -13)
Sertraline	N <sup>a</sup>		14	4	13
	Randomization	Mean (SD)	51.9 (46.9)	55.5 (26.1)	39.5 (23.6)
	Week 2	Mean (SD)	55.7 (42.2)	45.0 (25.3)	42.3 (35.4)
	Change	Mean (SD)	-0.4 (33.2)	3.8 (12.4)	4.7 (20.6)
	% Change	Mean (SD)	37.7 (88.8)	12.1 (24.0)	24.8 (70.4)
		Median (range)	23.7 (-45 to 273)	8.1 (-10 to 38)	11.4 (-68 to 209)
	Week 4	Mean (SD)	46.6 (29.5)	46.5 (38.2)	42.2 (24.2)
	Change	Mean (SD)	14.0 (22.1)	-1.2 (16.0)	0.3 (13.7)
	% Change	Mean (SD)	626.1 (1906.3)	-9.5 (28.6)	7.7 (38.0)
		Median (range)	20.3 (-76 to 6049)	-14.0 (-36 to 21)	4.6 (-42 to 55)

Plasma concentration levels and change from randomization to Weeks 2 and 4

Antidepressant			PLA N=75	QTP150 N=72	QTP300 N=68
Desmethyl-sertraline	N <sup>a</sup>		14	5	13
	Randomization	Mean (SD)	78.4 (51.0)	76.7 (47.1)	70.4 (61.6)
	Week 2	Mean (SD)	93.3 (60.1)	83.8 (38.2)	75.5 (67.8)
	Change	Mean (SD)	12.9 (20.6)	16.2 (18.3)	5.0 (18.8)
	% Change	Mean (SD)	24.0 (44.6)	220.0 (408.3)	17.1 (35.7)
		Median (range)	11.9 (-14 to 150)	25.8 (-3 to 832)	16.7 (-41 to 74)
	Week 4	Mean (SD)	75.4 (42.1)	99.5 (51.9)	72.4 (57.7)
	Change	Mean (SD)	14.5 (31.8)	13.9 (28.0)	2.5 (17.7)
	% Change	Mean (SD)	57.9 (125.8)	11.4 (25.7)	7.1 (33.2)
		Median (range)	10.4 (-47 to 377)	1.1 (-8 to 41)	-1.8 (-48 to 60)
	Venlafaxine	N <sup>a</sup>		10	10
Randomization		Mean (SD)	107.4 (72.9)	120.0 (75.0)	112.3 (116.3)
Week 2		Mean (SD)	130.4 (130.4)	92.5 (50.4)	113.4 (104.2)
Change		Mean (SD)	23.3 (61.0)	-34.4 (85.7)	-16.8 (76.1)
% Change		Mean (SD)	29.4 (89.0)	-13.6 (47.9)	143.3 (370.5)
		Median (range)	16.1 (-78 to 225)	-14.4 (-83 to 54)	9.6 (-72 to 1101)
Week 4		Mean (SD)	152.8 (111.6)	63.3 (49.8)	88.4 (64.0)
Change		Mean (SD)	9.2 (47.3)	-19.6 (68.3)	-13.5 (76.9)
% Change		Mean (SD)	7.1 (27.4)	-1.9 (71.2)	222.4 (598.7)
		Median (range)	21.3 (-37 to 29)	-28.9 (-83 to 95)	10.7 (-54 to 1575)

Plasma concentration levels and change from randomization to Weeks 2 and 4

Antidepressant			PLA N=75	QTP150 N=72	QTP300 N=68
<i>O</i> -desmethyl-venlafaxine	N <sup>a</sup>		10	10	13
	Randomization	Mean (SD)	229.7 (114.5)	178.2 (118.6)	169.9 (117.7)
	Week 2	Mean (SD)	248.3 (120.3)	218.1 (161.5)	178.0 (86.0)
	Change	Mean (SD)	32.0 (107.1)	34.9 (58.7)	-0.5 (100.3)
	% Change	Mean (SD)	23.6 (46.3)	19.1 (30.0)	37.6 (99.7)
		Median (range)	28.5 (-42 to 92)	24.9 (-35 to 63)	10.0 (-55 to 245)
	Week 4	Mean (SD)	249.2 (152.7)	170.2 (125.7)	182.0 (104.3)
	Change	Mean (SD)	4.4 (158.9)	21.2 (88.4)	-8.8 (122.8)
	% Change	Mean (SD)	12.2 (43.8)	14.9 (43.9)	34.9 (154.7)
		Median (range)	20.6 (-58 to 55)	19.4 (-46 to 59)	-0.1 (-93 to 406)

<sup>a</sup> Number of patients at randomization.

N Number of patients in treatment group. NA Not applicable. NAV Not available. NC Not calculated. PLA Placebo. QTP Quetiapine XR. SD Standard deviation.

Note: All units of measure are in ng/mL.

There was a range in interpatient antidepressant doses being used in this study, but the dose level for an individual patient was maintained throughout the study. Large variability in plasma concentrations was observed. The sponsor stated that the range in antidepressant doses between patients accounts for some of the variability observed in the reported mean plasma concentrations. The sponsor stated that for both the placebo and the quetiapine XR dose groups, the antidepressant and metabolite plasma concentrations did not demonstrate any consistent trend over the time of the study. The sponsor stated that although there was a great deal of variability in the plasma concentration data, there did not appear to be an association between the quetiapine XR dose being co-administered and the median relative change observed from baseline (randomization). For amitriptyline, PK evaluable data were available for only 1 patient, so the interpretability of that data is limited.

The sponsor stated that overall, there did not appear to be a consistent trend in the relative median change from baseline in the plasma concentrations of the antidepressants and their associated metabolites in the presence of co-administered quetiapine XR that would indicate significant drug interactions requiring dose-adjustment of the antidepressant.

Sponsor's conclusion: The sponsor concluded that exploratory analysis of the interaction between quetiapine XR and the antidepressants and their associated metabolites, within the inherent

limitations of obtaining appropriately timed PK sampling in an outpatient setting, revealed no apparent drug interactions requiring dose-adjustment of the antidepressant.

*Reviewer Comments: The effect of quetiapine on the anti-depressant evaluated when they are co-administered together was not conclusive from this exploratory study. The reviewer does not concur with the sponsor's conclusion that, there is no apparent interactions requiring dose adjustment. There was a very large variability in the data and evaluation of the individual data indicated some patients had large increases in their anti-depressant therapy. It is recommended that caution should be exercised when the two doses are administered together.*

**Title (D1448C00007):** A Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended-release (Seroquel XR™) in Combination with an Antidepressant in the Treatment of Patients with Major Depressive Disorder with Inadequate Response to an Antidepressant Treatment (Onyx Study)

**Objective:** The primary objective of the study was to evaluate the efficacy of quetiapine fumarate extended-release (in combination with an antidepressant versus an antidepressant in combination with placebo in patients with Major Depressive Disorder (MDD).

The secondary objectives were:

1. To evaluate if quetiapine XR in combination with an antidepressant improves health-related quality of life of patients with MDD, compared to an antidepressant in combination with placebo;
2. To evaluate if quetiapine XR in combination with an antidepressant reduces anxiety symptoms in patients with MDD, compared to an antidepressant in combination with placebo;
3. To evaluate if quetiapine XR in combination with an antidepressant improves sleep quality in patients with MDD, compared to an antidepressant in combination with placebo;
4. To evaluate if quetiapine XR in combination with an antidepressant is effective in reducing suicidal ideation in patients with MDD, compared to an antidepressant in combination with placebo;
5. To evaluate if quetiapine XR in combination with an antidepressant improves somatic symptoms in patients with MDD, compared to an antidepressant in combination with placebo;
6. To evaluate if quetiapine XR in combination with an antidepressant improves satisfaction with medication in patients with MDD, compared to an antidepressant in combination with placebo;
7. To evaluate if quetiapine XR in combination with an antidepressant is as safe and well-tolerated as an antidepressant in combination with placebo in the treatment of patients with MDD;
8. To evaluate if quetiapine XR in combination with an antidepressant changes the plasma level of antidepressant.

**Study Design (Pharmacokinetic subsection):** This was a 6-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled, double-dummy, phase III study of the efficacy and safety of quetiapine XR 150 mg/day and 300 mg/day in combination with an antidepressant in the treatment of patients with MDD who have shown an inadequate response to an antidepressant treatment. The patient population were male or female patients, 18 to 65 years old, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnosis of MDD, Single Episode (296.2x) or MDD, Recurrent (296.3x) as confirmed by the Mini-International Neuropsychiatric Interview (MINI). In addition, patients had to have a Hamilton Rating Scale for Depression (HAM-D) (17-item, hereafter referred to as HAM-D) total score  $\geq 20$  and a HAM-D Item 1 (depressed mood, hereafter referred to as HAM-D Item 1) score  $\geq 2$  at both enrollment and randomization.

The randomized treatment period was preceded by a washout period of up to 14 days. Patients continued to maintain the same antidepressant therapy from the period beginning at enrollment through the end of double-blind treatment. Patients should have been on treatment with 1 of the

following antidepressants for at least 6 weeks prior to enrollment (at least minimum effective antidepressant dose according to label), with at least 1 dose increase when permitted according to label:

- amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine.

All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. Patients in the quetiapine XR 150 mg/day–group maintained this dose through the end of the randomized treatment period. Patients in the quetiapine XR 300 mg/day–group were up-titrated to 300 mg/day on Day 5, and then maintained this dose through the end of the randomized treatment period. The ongoing treatment with the antidepressant was maintained at the same dose throughout the study. Study treatment was given in tablets of the following doses (lot #): quetiapine XR 50 mg (LJ4707, 41279H06, LM4625), quetiapine XR 300 mg (33419D05, 41280I06, LM4617), placebo 50-mg match (32195F05, 32200H05, 32201E05, 32202B05), and placebo 300-mg match (CP296X, CP297X).

Analytical Method: Fluoxetine and norfluoxetine were extracted using a liquid-liquid extraction procedure. The remaining analytes were extracted from human plasma using a solid phase extraction procedure. The extracts underwent liquid chromatography (LC) and the analytes were detected using tandem mass spectrometry (MS/MS) detection. Samples were analyzed using validated LC/MS/MS methods. The following table lists the calibration ranges that were validated in human plasma.

Summary of Calibration Ranges in Human Plasma

Analyte	LLOQ (ng/mL)	ULQ (ng/mL)
Amitriptyline	1.00	250
Nortriptyline	1.00	250
Bupropion	TBD	TBD
Hydroxybupropion	TBD	TBD
Erythrohydrobupropion	TBD	TBD
Threoxyhydrobupropion	TBD	TBD
Citalopram	0.500	250
Duloxetine	1.00	250
Fluoxetine	1.00	500
Norfluoxetine	1.00	500
Escitalopram	0.500	250
Paroxetine	1.00	250
Sertraline	1.00	250
Desmethylsertraline	1.00	250
Venlafaxine	1.00	250
O-Desmethylvenlafaxine	1.00	250

The general criteria for acceptance of standards and QC samples was based on %RE being within  $\pm 15\%$  for each standard and QC, except for the lower limit of quantitation standard and the lower limit of quantitation (LLOQ) QC, where the %RE was required to be within  $\pm 20\%$ . For each validation batch, at least 75% of the standards and 66% of the overall QC samples, including 50% at each concentration, were required to meet these criteria for the results to be considered acceptable. The analytical method was considered to be precise and accurate provided the inter-assay precision (%CV) and accuracy (%RE) were  $\leq 15\%$  and within  $\pm 15\%$ , respectively, with the exception of the LLOQ where  $\leq 20\%$  (%CV) and within  $\pm 20\%$  (%RE) were accepted. The following table contains the precision and accuracy table for calibration standards.

Precision and Accuracy Summary Table for Calibration Standards

Analyte	%CV Value		%RE Value	
	Minimum	Maximum	Minimum	Maximum
Amitriptyline	0.4	3.5	-2.8	2.7
Nortriptyline	1.1	5.0	-5.3	3.6
Bupropion	TBD	TBD	TBD	TBD
Hydroxybupropion	TBD	TBD	TBD	TBD
Erythrohydrobupropion	TBD	TBD	TBD	TBD
Threohydrobupropion	TBD	TBD	TBD	TBD
Citalopram	1.7	5.7	-4.4	3.0
Duloxetine	3.0	4.6	-6.0	4.8
Escitalopram	2.9	6.4	-3.2	2.3
Fluoxetine	3.6	10.7	-2.2	3.2
Norfluoxetine	2.1	9.5	-3.4	2.0
Paroxetine	2.6	6.0	-2.0	1.7
Sertraline	2.3	6.5	-1.6	2.5
Desmethylertraline	5.0	10.6	-2.3	3.9
Venlafaxine	1.9	11.2	-3.0	1.9
O-Desmethylvenlafaxine	1.7	4.1	-1.3	2.0

TBD To be determined

Precision and Accuracy Summary Table for QC Samples

Analyte	%CV Value		%RE Value	
	Minimum	Maximum	Minimum	Maximum
Amitriptyline	5.3	7.5	-4.4	2.3
Nortriptyline	4.1	8.8	-0.6	6.3
Bupropion	TBD	TBD	TBD	TBD
Hydroxybupropion	TBD	TBD	TBD	TBD
Erythrohydrobupropion	TBD	TBD	TBD	TBD
Threohydrobupropion	TBD	TBD	TBD	TBD
Citalopram	4.5	9.6	-3.9	4.7
Duloxetine	3.6	6.4	-6.1	-1.3
Escitalopram	2.2	3.2	-1.1	3.3
Fluoxetine	5.0	7.5	-6.6	10.7
Norfluoxetine	2.5	8.3	-6.6	4.3
Paroxetine	4.3	8.0	-0.6	3.3
Sertraline	3.9	7.1	-1.1	4.8
Desmethylertraline	6.5	10.2	-2.8	1.0
Venlafaxine	2.8	8.5	-0.6	5.0
O-Desmethylenlafaxine	3.3	5.5	-1.1	2.3

TBD To be determined.

Bupropion was extracted from human plasma using a solid phase extraction procedure. The extracts underwent liquid chromatography (LC) and the analyte was detected using tandem mass spectrometry (MS/MS) detection. The Bupropion calibration in human plasma range from 10 to 2000 ng/mL. The minimum and maximum values of accuracy (%RE) for calibration standards were -2.6 and 5.4, respectively. The minimum and maximum accuracy (%RE) values for Bupropion QC samples were -6.0 and -3.3, respectively. The analytical methods are acceptable.

Data Analysis: The relative mean change of the individual changes in plasma concentrations at Weeks 2 and 4 relative to the baseline concentration was calculated for each antidepressant and metabolite of interest. Where a baseline sample was missing or antidepressant concentrations were not quantifiable, the PK data for that subject were excluded from the analysis. The percent change from baseline was not calculated for Weeks 2 and/or 4 if a quantifiable antidepressant concentration was not available from that visit.

Results: Results of the analysis of the plasma concentration levels and change from randomization are shown in the following tables.

Plasma Concentration Levels and Change from randomization to Weeks 2 and 4

Antidepressant			PLA N=95	QTP150 N=101	QTP300 N=83
Amitriptyline	N <sup>a</sup>		1	1	1
	Randomization	Mean (SD)	42.0 (NC)	105.0 (NC)	38.2 (NC)
	Week 2	Mean (SD)	55.7 (NC)	154.0 (NC)	37.8 (NC)
	Change	Mean (SD)	13.7 (NC)	49.0 (NC)	-0.4 (NC)
	% change		32.6	46.7	-1.1
	Week 4	Mean (SD)	NA	127.0 (NC)	25.4 (NC)
	Change	Mean (SD)	NA	22.0 (NC)	-12.8 (NC)
	% change		NA	21.0	-33.5
Nortriptyline	N <sup>a</sup>		1	1	1
	Randomization	Mean (SD)	48.6 (NC)	52.7 (NC)	15.0 (NC)
	Week 2	Mean (SD)	60.2 (NC)	93.8 (NC)	14.4 (NC)
	Change	Mean (SD)	11.6 (NC)	41.1 (NC)	-0.6 (NC)
	% change		23.9	78.0	-4.0
	Week 4	Mean (SD)	NA	96.1 (NC)	12.9 (NC)
	Change	Mean (SD)	NA	43.4 (NC)	-2.1 (NC)
	% change		NA	82.4	-14.0
Citalopram	N <sup>a</sup>		17	25	12
	Randomization	Mean (SD)	75.4 (41.0)	65.0 (46.9)	75.6 (65.1)
	Week 2	Mean (SD)	82.5 (52.9)	72.1 (50.9)	83.3 (61.5)
	Change	Mean (SD)	7.0 (25.5)	5.7 (29.9)	6.5 (22.3)
	% change		5.1	21.6	51.7
	Week 4	Mean (SD)	83.1 (57.0)	56.5 (61.3)	73.4 (58.1)
	Change	Mean (SD)	3.9 (36.2)	9.0 (50.4)	-6.5 (21.4)
	% change		4.5	13.3	29.2

<sup>a</sup> Number of patients at randomization.

N Number of patients in treatment group. NA Not applicable. NC Not calculated. PLA Placebo.

QTP Quetiapine XR. SD Standard deviation.

Note: All units of measure are in ng/mL.

Plasma Concentration Levels and Change from randomization to Weeks 2 and 4

Duloxetine	N <sup>a</sup>		6	6	7
	Randomization	Mean (SD)	37.7 (24.2)	37.5 (28.1)	65.8 (43.0)
	Week 2	Mean (SD)	34.5 (23.0)	36.1 (30.1)	42.2 (36.4)
	Change	Mean (SD)	-3.2 (16.2)	8.3 (13.1)	-15.8 (39.7)
	% change		-1.3	64.5	-14.0
	Week 4	Mean (SD)	48.5 (44.8)	50.7 (47.5)	35.3 (17.3)
	Change	Mean (SD)	-0.4 (32.6)	7.7 (56.6)	-30.4 (32.4)
	% change		-8.4	51.3	-32.2
Escitalopram	N <sup>a</sup>		20	14	18
	Randomization	Mean (SD)	23.9 (11.7)	26.8 (20.7)	30.5 (14.4)
	Week 2	Mean (SD)	26.0 (18.4)	30.9 (20.5)	28.1 (13.7)
	Change	Mean (SD)	0.8 (11.0)	-0.1 (5.2)	-1.0 (11.8)
	% change		16.8	2.5	3.3
	Week 4	Mean (SD)	20.3 (12.6)	34.3 (29.4)	29.4 (16.0)
	Change	Mean (SD)	-3.2 (9.0)	7.7 (18.6)	-1.0 (12.3)
	% change		-9.1	38.1	3.7
Fluoxetine	N <sup>a</sup>		6	9	9
	Randomization	Mean (SD)	125.0 (114.3)	135.7 (110.0)	158.6 (147.8)
	Week 2	Mean (SD)	151.5 (107.6)	120.3 (85.2)	144.1 (140.1)
	Change	Mean (SD)	15.8 (41.6)	18.1 (32.4)	-0.1 (31.7)
	% change		42.2	46.2	54.2
	Week 4	Mean (SD)	173.9 (99.9)	169.1 (118.2)	193.0 (171.2)
	Change	Mean (SD)	38.1 (86.0)	34.0 (56.4)	18.1 (32.4)
	% change		71.4	65.6	100.9

<sup>a</sup> Number of patients at randomization.

N Number of patients in treatment group. NA Not applicable. NC Not calculated. PLA Placebo.

QTP Quetiapine XR. SD Standard deviation.

Note: All units of measure are in ng/mL.

Plasma Concentration Levels and Change from Randomization to Weeks 2 and 4

Norfluoxetine	N <sup>a</sup>		6	9	9
	Randomization	Mean (SD)	153.4 (101.9)	123.8 (101.6)	122.7 (95.9)
	Week 2	Mean (SD)	168.8 (100.4)	98.0 (60.4)	105.2 (63.1)
	Change	Mean (SD)	13.4 (34.5)	15.7 (25.6)	3.9 (19.3)
	% change		38.6	114.7	89.6
	Week 4	Mean (SD)	188.0 (86.6)	137.2 (108.1)	152.4 (101.7)
	Change	Mean (SD)	20.5 (64.3)	14.9 (64.2)	12.1 (21.3)
	% change		18.4	139.8	114.5
Paroxetine	N <sup>a</sup>		11	6	4
	Randomization	Mean (SD)	104.1 (105.2)	111.0 (82.3)	98.3 (117.7)
	Week 2	Mean (SD)	100.6 (118.4)	135.6 (87.3)	98.3 (57.2)
	Change	Mean (SD)	0.3 (16.8)	24.6 (48.7)	0.1 (88.6)
	% change		9.7	81.3	64.4
	Week 4	Mean (SD)	108.8 (101.0)	87.9 (53.0)	192.6 (241.0)
	Change	Mean (SD)	4.7 (32.8)	-23.1 (63.8)	51.3 (56.1)
	% change		17.2	3.8	71.4
Sertraline	N <sup>a</sup>		17	21	17
	Randomization	Mean (SD)	39.2 (20.3)	49.2 (31.9)	38.1 (31.1)
	Week 2	Mean (SD)	41.6 (19.0)	42.5 (31.9)	32.5 (24.7)
	Change	Mean (SD)	2.4 (16.2)	-6.7 (14.3)	5.6 (16.8)
	% change		24.0	-5.1	27.8
	Week 4	Mean (SD)	45.1 (25.7)	40.7 (30.5)	37.0 (32.1)
	Change	Mean (SD)	8.5 (17.4)	-6.7 (12.0)	-1.1 (13.8)
	% change		30.0	-17.9	7.4

<sup>a</sup> Number of patients at randomization.

N Number of patients in treatment group. NA Not applicable. NC Not calculated. PLA Placebo.

QTP Quetiapine XR. SD Standard deviation.

Note: All units of measure are in ng/mL.

Plasma Concentration Levels and Change from Randomization to Weeks 2 and 4

Desmethyl sertraline	N <sup>a</sup>		17	21	17
	Randomization	Mean (SD)	69.4 (30.9)	81.9 (53.1)	64.2 (56.5)
	Week 2	Mean (SD)	84.2 (34.8)	81.6 (55.2)	59.3 (44.6)
	Change	Mean (SD)	14.8 (26.9)	-0.2 (24.9)	13.8 (26.1)
	% change		46.0	32.2	32.8
	Week 4	Mean (SD)	87.3 (46.7)	76.3 (53.8)	72.1 (51.6)
	Change	Mean (SD)	19.3 (32.7)	-0.9 (30.7)	7.9 (30.1)
	% change		47.3	9.8	25.2
	Venlafaxine	N <sup>a</sup>		17	19
Randomization		Mean (SD)	166.5 (236.9)	82.7 (72.6)	107.0 (102.6)
Week 2		Mean (SD)	214.4 (299.8)	58.0 (43.6)	64.4 (58.5)
Change		Mean (SD)	47.9 (128.4)	-20.5 (54.6)	-33.4 (63.7)
% change			45.4	6.6	42.2
Week 4		Mean (SD)	159.5 (222.7)	78.6 (56.0)	80.6 (119.6)
Change		Mean (SD)	-35.6 (62.8)	-11.0 (40.9)	-41.4 (88.8)
% change			-19.6	2.0	-39.1
<i>O</i> -desmethyl- venlafaxine		N <sup>a</sup>		17	19
	Randomization	Mean (SD)	214.6 (128.7)	264.0 (149.4)	232.2 (135.9)
	Week 2	Mean (SD)	238.2 (129.3)	229.4 (184.5)	196.1 (127.8)
	Change	Mean (SD)	23.6 (66.9)	-25.0 (132.2)	-23.4 (113.6)
	% change		20.6	-3.8	7.0
	Week 4	Mean (SD)	255.9 (189.9)	251.4 (163.4)	195.5 (179.0)
	Change	Mean (SD)	24.6 (97.6)	4.6 (68.4)	-27.1 (110.5)
	% change		11.0	5.4	-13.5

<sup>a</sup> Number of patients at randomization.

N Number of patients in treatment group. NA Not applicable. NC Not calculated. PLA Placebo.

QTP Quetiapine XR. SD Standard deviation.

Note: All units of measure are in ng/mL.

There was a range in intersubject antidepressant doses being used in this study, but the dose level for an individual subject was maintained throughout the study.

For both the placebo and the quetiapine XR dose groups antidepressant and metabolite plasma concentrations did not demonstrate any consistent trend over the time of the study. While there was a great deal of variability in the plasma concentration data, the sponsor reported that there did not appear to be an association between the quetiapine XR dose being co-administered and the median relative change observed from baseline (or time of randomization into the study). The sponsor reported that the analysis of relative change from baseline (%) is very dependent of the baseline concentration value. Therefore, instances where large relative changes were observed, a low plasma concentration value was attained at baseline suggesting a possible previous lack of compliance with the subject's antidepressant therapeutic regimen.

The sponsor concluded that, overall, there did not appear to be a consistent trend in the relative mean change from baseline in the plasma concentrations of the antidepressants and their associated metabolites in the presence of quetiapine XR that would indicate that co-administration of quetiapine had resulted in significant drug interactions.

**Safety Summary:** The sponsor reported that the overall incidence of AEs was highest in the quetiapine XR 300-mg/day group, followed by the quetiapine XR 150-mg/day and placebo groups. Most AEs were mild to moderate in severity. There were no deaths among the patients assigned to randomized treatment; 1 death occurred prior to randomization. The incidence of SAEs in the quetiapine XR treatment groups was low (<2%) and similar to placebo. The number of patients with AEs considered by the investigator to be possibly related to study treatment was higher in the quetiapine XR groups than in the placebo group, and appeared to be dose-related. Similarly, the number of patients withdrawing from the study due to an AE was higher in the quetiapine XR groups compared to placebo and appeared to be related to dose. The pattern of common AEs observed in the quetiapine XR treatment groups generally conformed to that which was anticipated based on the known pharmacological profile of quetiapine. The most common AEs in the quetiapine XR groups were dry mouth, somnolence, fatigue, sedation, and dizziness, and occurred at a higher incidence compared to placebo.

*Reviewer's comments: The percentage of change in antidepressants was calculated for each patient and the mean of the percent change computed and reported in the tables above. The percentage of change in antidepressants after co-administration of quetiapine was highly variable for different patients and drugs. The highest variation was seen on patients on fluoxetine. Due to the high variability in the data, definite conclusions cannot be drawn from this data. Therefore, it is recommended that patients be observed closely when these anti-depressants are administered and doses of anti-depressants adjusted accordingly.*

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BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

**OTHER REVIEW(S)**

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

**DATE:** December 3, 2008

**TO:** Kofi Ansah, Regulatory Project Manager  
Earl Hearst, Medical Officer  
Division of Psychiatry Products

**FROM:** John Lee, Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

**THROUGH:** Tejashri Purohit-Sheth, MD  
Branch Chief, Good Clinical Practice Branch II  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** NDA 22-047 SE 10/11/12

**APPLICANT:** Astra Zeneca Pharmaceuticals LP

**DRUG:** Quetiapine Fumarate Extended Release Tablets (Seroquel XR)

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Standard

**INDICATIONS:** Single, adjunctive, or maintenance therapy of major depressive disorder

**CONSULTATION REQUEST DATE:** May 15, 2008

**DIVISION ACTION GOAL DATE:** December 5, 2008

**PDUFA DATE:** December 27, 2008

## **I. BACKGROUND**

### Major Depressive Disorder

Major Depressive Disorder (MDD) is characterized by the presence of one or more depressive episodes without manic, mixed, or hypo-manic episodes. The major depressive episode must be present for at least two weeks and must represent a change from previous functioning. Major depressive episodes may begin at any age (average age of onset in the mid-twenties). MDD affects about 120 million people worldwide and is among the leading causes of disability worldwide.

Up to 15% of patients with severe major depressive episodes commit suicide. Compared with the general population, patients with MDD have higher medical morbidity, pain and physical illness and lower social, occupational, and educational functioning. The lifetime risk for MDD is about 5 to 12% for men and 10% to 25% for women. There is increasing evidence for a genetic component in the development of MDD but clear pattern of transmission has not been elucidated.

Antidepressant medications have become the first line treatment of MDD, and there are currently more than 25 agents approved in the US for the treatment of MDD. Newer agents (selective serotonin reuptake inhibitors, serotonin-norepinephrine dual reuptake inhibitors) have replaced older agents (tricyclic antidepressants, monoamine oxidase inhibitors). Although the newer agents are easier to use and have lower cardiac toxicity (decreased potential for lethal overdose) than their predecessors, they remain ineffective in up to nearly a fourth of patients with MDD.

### Quetiapine Fumarate (Seroquel)

Quetiapine is not a new molecular entity (NME) and has been previously approved in the US for the treatment of schizophrenia and bipolar disorder, as follows:

- Quetiapine immediate-release (IR)
  - Schizophrenia, 1997
  - Mania associated with bipolar disorder, 2003
  - Depression associated with bipolar disorder, 2006
- Quetiapine extended-release (XR)
  - Schizophrenia, 2007
  - Mania associated with bipolar disorder (NDA 22-047 currently under review)
  - Depression associated with bipolar disorder (NDA 22-047 currently under review)

To date there is minimal data regarding the efficacy of quetiapine in the treatment of MDD. In patients with schizophrenia, quetiapine IR has been shown to improve depressive symptoms independently of their effect on psychotic symptoms. These studies (D1448C00002, D1448C00005, and D1448C00006) show that quetiapine XR is safe and effective in MDD.

### Study Sites and Protocols

Three clinical sites were selected for inspection. Each site was the largest in each of the three studies that supported a new indication.

#### **Study D1448C00002 (Site 1013)**

- This was an eight-week multi-center, double blind, randomized, placebo and active (duloxetine 60 mg) controlled study of the efficacy and safety of quetiapine XR 150 mg and 300 mg in the treatment of patients with major depressive disorder (MDD).
- The study consisted of an up to 28-day enrollment period (washout of prior therapy), a 6-week treatment period (one of four treatment regimens: quetiapine XR 150 mg, quetiapine XR 300 mg, duloxetine 60 mg, or placebo), and a 2-week post-treatment period (reinstitute baseline therapy).
- The primary efficacy endpoint was the change from baseline in Montgomery-Asberg Depression rating Scale (MADRS) total score at Week 6. Each of approximately 36 centers in the United States were to enroll 10 - 25 patients, men and women (age 18 to 65) with moderate to severe MDD.

#### **Study D1448C00006 (Site1019)**

- This was an eight-week multi-center, double blind, randomized, placebo controlled study of the efficacy and safety of quetiapine XR 150 mg and 300 mg in combination with an antidepressant in the treatment of patients with MDD who have shown an inadequate response to the antidepressant treatment.
- The study consisted of an up to 14-day enrollment period (washout of prior therapy), a 6-week treatment period (one of three treatment regimens: quetiapine XR 150 mg, quetiapine XR 300 mg, or placebo), and a 2-week post-treatment period (reinstitute baseline therapy).
- The primary efficacy endpoint was the change from baseline in Montgomery-Asberg Depression rating Scale (MADRS) total score at Week 6. Each of approximately 25 centers in the United States was to enroll 15 - 25 patients, men and women (age 18 to 65) with moderate to severe MDD.

#### **Study D1448C00005 (Site1037)**

- This was a 52-week multi-center, double blind, placebo controlled, randomized withdrawal study of the efficacy and safety of quetiapine XR in the treatment of patients with MDD.
- The study consisted of four periods: (1) enrollment of up to 28 days, (2) open-label run-in of 4 to 8 weeks, (3) open-label stabilization treatment of at least 16 weeks, and (4) randomized treatment of up to 52 weeks. Patients were randomized to quetiapine XR or matching placebo at the same dose as at end of open-label stabilization. At randomization, open-label quetiapine XR were replaced with blinded quetiapine XR or placebo.
- The primary efficacy endpoint was the time to a MDD event after entering the randomized treatment period. Each of approximately 300 centers in the United States were to enroll 5 - 15 patients, men and women (age 18 to 65) with moderate to severe MDD.

**II. INSPECTION RESULTS**

	Clinical Study Site	Site Protocol Subjects	Inspection Dates	Classification	
				Field	Final
1	Linda Harper, MD Clinical Neurosciences Solutions, Inc. 77 West Underwood Street, 3rd Floor Orlando, FL 32806	Site 1013 D1448C00002 60 subjects	Oct 2 - 8, 2008	NAI	NAI
2	Miguel Flores, MD Berma Research Group 7150 West 20th Avenue, Suite 515 Hialeah, FL 33016	Site 1037 D1448C00005 18 subjects	Nov 4 - 6, 2008	NAI	pending
3	Ronald Brenner, MD Neurobehavioral Research Inc. 74 Carman Avenue Cedarhurst, NY 11516	Site1019 D1448C00006 29 subjects	Aug 26 - Sep 4, 2008	NAI	NAI

NAI = no action indicated (no deviations from regulations); VAI = voluntary action indicated (no significant deviations from regulations); OAI = official action indicated (significant deviations from regulations); NA = not applicable

Classification:

Field = field investigator's initial recommendation in classifying the inspection result

Final = CDER's final classification of the inspection result

**1. Linda Harper, MD (Site 1013): NAI**

Clinical Neurosciences Solutions, Inc.  
77 West Underwood Street, 3rd Floor  
Orlando, FL 32806

## a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, and adherence to protocol and applicable regulations.
- Data verification: primary efficacy endpoint data, adverse event data and reporting, protocol deviations, and subject discontinuation
- Subjects: 76 subjects were screened, 60 enrolled in study D1448C00002, and 33 completed the study. Complete records were reviewed for 14 subjects.

- b. General observations and commentary: No major deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring by Lineberry Research Associates (contract research association) appeared to be adequate. Minor but noteworthy non-compliance with applicable Good Clinical Practice (GCP) regulations was limited to an apparently isolated finding: in three subjects, the time period between screening and enrollment was longer (by as many as 3 days) than the protocol-specified time interval (14 days).

- c. Assessment of data integrity: Data from this study site (Site 1013, Study D1448C00002) appear reliable.

**2. Miguel Flores, MD (Site 1037): NAI**

Berma Research Group  
7150 West 20th Avenue, Suite 515  
Hialeah, FL 33016

- a. What was inspected:
  - Scope of inspection: subject eligibility, informed consent, study monitoring, test article accountability and disposition, IRB oversight, and adherence to protocol and applicable regulations.
  - Data verification: primary efficacy endpoint data, adverse event data and reporting, protocol deviations, and subject discontinuation.
  - Subjects: 40 subjects were screened, 18 enrolled in study D1448C00005, and 18 completed the study. Complete records were reviewed for all 18 subjects.
- b. General observations and commentary: No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate. No significant non-compliance with applicable GCP regulations or the study protocol was noted.
- c. Assessment of data integrity: Data from this study site (Site 1037, Study D1448C00005) appear reliable.

**3. Ronald Brenner, MD (Site 1019): NAI**

Neurobehavioral Research Inc.  
74 Carman Avenue  
Cedarhurst, NY 11516

- a. What was inspected:
  - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations, study monitoring, and IRB oversight.
  - Data verification: primary efficacy endpoint data, adverse event data and reporting, protocol deviations, and subject discontinuation.
  - Subjects: 31 subjects were screened and 29 enrolled in study D1448C00006. Complete records were reviewed for 12 subjects.
- b. General observations and commentary: No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring were adequate.
- c. Assessment of data integrity: Data from this study site (Site 1019, Study D1448C00006) appear reliable.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

No significant deficiencies were observed at the three clinical sites selected for inspection in support of NDA 22-047 (SE 10/11/12). A Form FDA 483 was not issued at any of the clinical sites, for any of the three studies (D1448C00002, D1448C00005, and D1448C00006). The minor deficiencies observed were apparently isolated, did not suggest bias in study conduct, and are not expected to importantly affect data integrity. The data generated from the three study sites inspected are considered acceptable in support of the proposed indications.

**Note:** The final inspection report for Site 1037 (Dr. Miguel Flores) is pending as of December 8, 2008. Upon receipt and review of the final inspection report, an addendum to this clinical inspection summary will be provided if additional observations of clinical or regulatory significance are discovered.

{ See appended electronic signature page }

John Lee, MD  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Joseph P. Salewski  
Deputy Director  
Division of Scientific Investigations  
Office of Compliance

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John Lee  
12/3/2008 02:26:14 PM  
MEDICAL OFFICER

Joseph Salewski  
12/3/2008 02:38:43 PM  
CSO

**REGULATORY PROJECT MANAGER  
LABELING REVIEW**

Date: December 2, 2009

Drug/NDA: Seroquel XR (quetiapine fumarate) Extended-Release Tablets

Sponsor: AstraZeneca

Indication: Adjunctive Therapy to Antidepressants in Patients with Major Depressive Disorder (MDD)

Supplements under review:

NDA	Supplement	Received	Proposed Action
<b>Seroquel XR (quetiapine fumarate) Extended-Release Tablets</b>			
022047	SLR-016	12-19-07	Ack/Retain
022047	SLR-017	7-11-08	Ack/Retain
022047	SLR-019	9-11-08	Ack/Retain
022047	SLR-022	12-15-08	Ack/Retain
(b) (4)			
022047	SE1-011	6-2-09	Approval
(b) (4)			

**Background:**

1. Last approved labeling, submitted December 19, 2007 for S-006/007/008, was approved on October 8, 2008.
2. The sponsor submitted labeling supplement S-016 on December 19, 2007, adding information on the use of Seroquel XR in elderly patients with dementia in the Medication Guide.
3. The sponsor submitted labeling supplement S-017 on July 11, 2008, to include information regarding abnormal dreams/nightmares and increased creatine phosphokinase to the Adverse Reactions section under Clinical Study Experience (6.1).
4. The sponsor submitted labeling supplement S-019 on September 11, 2008, to include information regarding (b) (4)
5. The sponsor submitted labeling supplement S-022 on December 15, 2008, to include pediatric data regarding safety and the addition of falls and elevations in prolactin. Revisions were made to Sections 5.5 (Orthostatic hypotension), 5.12 (Hyperprolactinemia), 5.14 (Cognitive/Motor Impairment) (b) (4) (Use in children & adolescents), (b) (4) 8.4 (Pediatric Use [several additions of safety language]).
6. The sponsor submitted label revisions on January 26, 2009, based on comments for S-022, sent to the sponsor on December 18, 2008.

7. AstraZeneca submitted S-010/S-011/S-012, on February 27, 2008, to add new indications of:
  - a. S-010 Acute Treatment as Monotherapy of MDD
  - b. S-011 Adjunctive Treatment of MDD
  - c. S-012 Maintenance Treatment of MDD
8. A Complete Response (CR) letter was issued on December 22, 2008, to all three supplements. The CR letter cited longer term risks of metabolic abnormalities and risks of tardive dyskinesia.
9. The sponsor responded (b) (4) to the CR letter in a Class 2 resubmission dated June 2, 2009.

## **REVIEW**

### **22-047/SLR-016**

**Date: 12-19-07**

**CBE: No**

**Reviewed by Medical Officer: Yes**

This supplement adds a warning to the medication guide with regards to use of Seroquel XR in elderly patients with dementia. Please note that underline indicates addition to the approved medication guide.

### **Serious side effects may happen when you take SEROQUEL, including:**

- **Risk of death in the elderly with dementia: Medicines like SEROQUEL can raise the risk of death in elderly people who have lost touch with reality due to confusion and memory loss (dementia). SEROQUEL is not approved for treating psychosis in the elderly with dementia.**

### **22-047/SLR-017**

**Date: 7-11-08**

**CBE: Yes**

**Reviewed by Medical Officer: Yes**

This supplement provided for the following changes. Please note that strikethrough indicates deletion and underline indicates addition to the approved label:

1. Changed title of (b) (4) **Cholesterol and Triglyceride Elevations** to (b) (4) **Hyperlipidemia** to be consistent with the **Highlights Section**
2. Revision of **'6.1 Clinical Studies Experience'** under **Section 6 Adverse Reactions:**

(b) (4)

3. Removed the term (“restless legs”) from (b) (4) **Post Marketing Experience’** from **Section 6 Adverse Reactions:**

(b) (4)

**22-047/SLR-019**

**Date: 9-11-08**

**CBE: Yes**

**Reviewed by Medical Officer: Yes**

This supplement provided for the addition of information on thrombocytopenia to **Section 6.3 Post-Marketing Experience**. Please note that strikethrough indicates deletion and underline indicates addition to the approved label:

Other adverse reactions reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomyopathy hyponatremia, myocarditis rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), ~~and~~ Stevens-Johnson syndrome (SJS), and decreased platelets.

**22-047/SLR-022**

**Date: 12-15-08**

**CBE: Yes**

**Reviewed by Medical Officer: Yes**

This supplement provided for the following changes. Please note that strikethrough indicates deletion and underline indicates addition to the approved label:

1. Added information on falls in **Section 5.8 Orthostatic Hypotension**

Quetiapine may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its  $\alpha$ 1-adrenergic antagonist properties. Syncope was reported in 0.3% (b) (4) of the

patients treated with SEROQUEL XR, (b) (4)

2. Editorial correction of 954 patients in **Section (b) (4) Seizures**

(b) (4)

3. Made changes to **Section 5.13 Hyperprolactinemia**

(b) (4)

4. Per FDA request, changes were made to combine “somnolence” and “sedation” in **Section 5.16 Cognitive/Motor Impairment**

(b) (4)

5. Per FDA request, information on Use in Children and Adolescents was moved to **Section 8.4 Pediatric Use**. The following verbiage in what was formerly (b) (4) fully described in **Section 8.4**.

(b) (4)

(b) (4)

6. (b) (4) 8.4 (Pediatric Use [several additions of safety language])

## CONCLUSIONS

1. A side by side review found no changes other than those specified by the sponsor and provides for the above labeling changes when compared to the last approved labeling for Seroquel XR.
2. The clinical team reviewed the labeling changes proposed in S-016/S-017/S-019/S-022, and found them acceptable. Supplements S-016/S-017/S-019/S-022 will be acknowledged and retained in the approval letter for Supplement S-011.

(b) (4)

4. The Agency's proposed language for S-011 were communicated to the sponsor in an e-mail dated 11-23-09, and the sponsor responded with small revisions in an e-mail communication dated 12-1-09, to which FDA reviewed and found unobjectionable.
5. (b) (4)
6. An Approval action letter has been prepared for NDA 22-047/S-011

*{See appended electronic signature page}*

Juliette Touré, Pharm.D.  
Senior Regulatory Project Manager

*{See appended electronic signature page}*

Steven Hardeman, R.Ph., CPMS

Attachment: Annotated labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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(b) (4)

NDA-22047	SUPPL-11	ASTRAZENECA PHARMACEUTICA LS LP	SEROQUEL XR
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(b) (4)

NDA-22047	SUPPL-16	ASTRAZENECA PHARMACEUTICA LS LP	SEROQUEL XR
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NDA-22047	SUPPL-17	ASTRAZENECA PHARMACEUTICA LS LP	SEROQUEL XR
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NDA-22047	SUPPL-19	ASTRAZENECA PHARMACEUTICA LS LP	SEROQUEL XR
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NDA-22047	SUPPL-22	ASTRAZENECA PHARMACEUTICA LS LP	SEROQUEL XR
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JULIETTE T TOURE  
12/02/2009

STEVEN D HARDEMAN  
12/02/2009



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: August 28, 2009

To: Thomas Laughren, MD, Director  
**Division of Psychiatry Products**

Through: Jodi Duckhorn, MA, Team Leader  
**Division of Risk Management**

From: Latonia M. Ford, RN, BSN, MBA  
Patient Product Information Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling, Medication Guide

Drug Name(s): Seroquel (quetiapine fumarate) Tablets  
Seroquel XR (quetiapine fumarate) Extended-Release Tablets

Application Type/Number: NDA 20639/S-045, S-046  
NDA 22047/(b) (4) S-11 (b) (4)

Applicant/sponsor: Astra Zeneca Pharmaceuticals

OSE RCM #: 2009-1252  
2009-1358

## **1. INTRODUCTION**

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Seroquel (quetiapine fumarate) Tablets and Seroquel XR (quetiapine fumarate) Extended-Release Tablets. Please let us know if DPP would like a meeting to discuss this review or any of or changes prior to sending to the Applicant. DRISK's review of the proposed REMS will be provided to DPP under separate cover.

## **2. MATERIAL REVIEWED**

- Draft Seroquel (quetiapine fumarate) Tablets Prescribing Information (PI) submitted October 28, 2008 and revised by the Review Division throughout the current review cycle.
- Draft Seroquel (quetiapine fumarate) Tablets Medication Guide (MG) submitted on July 2, 2009.
- Draft Seroquel XR (quetiapine fumarate) Extended-Release Tablets Prescribing Information (PI) submitted June 2, 2009 and revised by the Review Division throughout the current review cycle.
- Draft Seroquel XR (quetiapine fumarate) Extended-Release Tablets submitted June 2, 2009

## **3. RESULTS OF REVIEW**

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

16 Pages Immediately Following Withheld - b(4) Draft Labeling

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/s/  
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LATONIA M FORD  
08/28/2009

JODI M DUCKHORN  
08/28/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

**RISK ASSESSMENT and RISK MITIGATION**  
**REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: November 19, 2009

To: Thomas Laughren, M.D., Director  
**Division of Psychiatry Products (DPP)**

Through: Claudia Karwoski, PharmD, Director  
**Division of Risk Management (DRISK)**

From: Jessica M. Diaz, RN, BSN, Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): SEROQUEL XR (quetiapine fumarate) extended-release tablets

Application Type/Number: NDA 22-047/ S-011

Applicant/sponsor: AstraZeneca Pharmaceuticals LP

OSE RCM #: 2009-1358

## 1 INTRODUCTION

This memorandum is in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document for SEROQUEL XR (quetiapine fumarate) extended-release tablets.

AstraZeneca submitted a supplemental new drug application for SEROQUEL XR on February 27, 2008 for the treatment of patients with major depressive disorder. The FDA sent a Complete Response Letter on December 22, 2008 requesting additional information on the long term risks. The supplement was discussed at an Advisory Committee meeting April 8, 2009. Astra Zeneca submitted a (b) (4) Response on June 2, 2009. The FDA notified Astra Zeneca on November 4, 2009 that a REMS would be required for SEROQUEL XR to ensure benefits outweigh potential risks of hyperglycemia, hyperlipidemia and weight gain. Astra Zeneca submitted their Proposed REMS and REMS Supporting Document on November 17, 2009.

Below are our comments on the proposed REMS. Please send these comments to the Applicant and request a response within two weeks of receipt. Please let us know if you would like a meeting to discuss these comments before sending to the Applicant. DRISK's review of the Medication Guide was sent to DPP under separate cover dated August 28, 2009. The DRISK review of the methodology and survey instruments once submitted by the Applicant to evaluate the REMS will be provided under separate cover.

## 2 MATERIAL REVIEWED

- SEROQUEL (quetiapine fumarate) Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated November 4, 2009
- Proposed SEROQUEL (quetiapine fumarate) Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on November 17, 2009

## 3 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of this Medication Guide-only REMS.

Please note, the timetable for submission of the assessments is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments **do not** need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

## Comments to AstraZeneca Pharmaceuticals LP:

See the appended SEROQUEL XR (quetiapine fumarate) REMS proposal (Appendix A of this memo) for track changes corresponding to comments in this review.

a. GOAL

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of SEROQUEL XR (quetiapine fumarate) Extended-Release Tablets.

b. We have some editorial comments for the Medication Guide distribution plan in this proposed REMS.

c. We acknowledge your plan to include a statement on each container or package of SEROQUEL XR (quetiapine fumarate) to instruct authorized dispensers to provide a medication guide to each patient under 21 CFR 208.24 (d). (b) (4)

(b) (4)

d. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable. We have some editorial comments in this section of the proposed REMS.

e. We acknowledge your plan to conduct a survey of patients in the REMS Supporting Document. Please submit for review a detailed plan to evaluate patients' understanding about the safe use of SEROQUEL XR (quetiapine fumarate). This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS Correspondence." If you plan to conduct this assessment using a survey, your submission should include:

- All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of SEROQUEL XR (quetiapine fumarate). This should include, but not be limited to:
  - Sample size and confidence associated with that sample size
  - How the sample will be determined (selection criteria)
  - The expected number of patients to be surveyed
  - How the participants will be recruited
  - How and how often the surveys will be administered
  - Explain controls used to minimize bias

- Explain controls used to compensate for the limitations associated with the methodology
- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Please let us know if you have any questions.

**2 Pages Immediately Following Withheld - b(4)**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22047	SUPPL-11	ASTRAZENECA PHARMACEUTICA LS LP	SEROQUEL XR

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/s/

JESSICA M DIAZ  
11/19/2009

CLAUDIA B KARWOSKI  
11/19/2009  
concur

## Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Office of Drug Evaluation I  
Division of Psychiatry Products

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**NDA#:** 022047/S011  
**Product:** Seroquel XR Tablets (quetiapine fumarate) Extended-Release Tablets  
**APPLICANT:** AstraZeneca  
**FROM:** Thomas Laughren, M.D., Director, Division of Psychiatry Products  
**DATE:** November 4, 2009

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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

Since Seroquel XR (quetiapine fumarate) was approved on May 17, 1997, we have become aware of additional clinical trial data and postmarketing safety data that show a risk of hyperglycemia, hyperlipidemia, and weight gain associated with all forms of Seroquel XR (quetiapine fumarate) in all patient populations. We consider this information to be “new safety information” as defined in section 505-1(b) of FDCA.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology (OSE), we have determined that a REMS is necessary for Seroquel XR (quetiapine fumarate) to ensure that the benefits of Seroquel XR (quetiapine fumarate) outweigh its risks. In reaching this determination, we considered the following:

- A. Major Depressive Disorder (MDD) affects approximately 14.8 million adults in the U.S. or about 6.7% of the adult U.S. population in a given year (Kessler RC, Chiu WT, Demler O, and Walters EE). MDD is the leading cause of disability in the U.S. for ages 15-44 (World Health Organization. The World Health Report 2004).
- B. MDD is a serious medical illness that is often chronic and debilitating. The symptoms and functional impairments associated with MDD can affect many aspects of a

patient's life. MDD is associated with increased risk of medical illness, including cardiovascular disease. In addition, it is associated with reduced life expectancy. Moreover, there is a significant risk of suicide in patients with MDD.

Until FDA approves this pending NDA supplement for Seroquel XR (quetiapine fumarate) as adjunctive therapy with antidepressants in MDD, there are limited therapeutic options approved for patients who have not responded adequately to standard antidepressant treatment.

- C. Seroquel XR (quetiapine fumarate) demonstrated efficacy in two placebo-controlled trials in adult patients with MDD who had not responded adequately to standard antidepressant treatment. Subjects in the Seroquel XR (quetiapine fumarate) and placebo groups continued concurrent treatment with standard antidepressants. In both studies, Seroquel XR (quetiapine fumarate) significantly reduced depressive symptoms. Adjunctive treatment with Seroquel XR (quetiapine fumarate) in the patient population studied could offer substantial benefit in reducing symptoms and functional impairment associated with MDD.
- D. The expected duration of therapy with Seroquel XR (quetiapine fumarate) in patients who obtain a clinical response would be at least 6 months to a year, for a single episode of MDD. Patients with recurrent episodes usually benefit from and require chronic maintenance treatment over many years.
- E. Several safety concerns have been identified in the clinical study programs for Seroquel XR (quetiapine fumarate). Potential risks include weight gain, hyperlipidemia, hyperglycemia, tardive dyskinesia and other extrapyramidal symptoms, and suicidality (antidepressant class effect associated in certain age groups). The safety findings in the MDD adjunctive therapy trials demonstrated that the safety profile of the drug was essentially identical to the safety profiles of Seroquel XR (quetiapine fumarate) treatment in other indications. There were no new or unexpected safety signals in the MDD program.

The current Seroquel XR (quetiapine fumarate) label contains warning language describing drug-related hyperglycemia, diabetes mellitus, weight gain, and lipid elevation. The label also contains the standard boxed warning and other warning language regarding suicidality. The risk of suicidality has been addressed in the existing Medication Guide for Seroquel XR (quetiapine fumarate).

- F. Seroquel XR (quetiapine fumarate) is not a new molecular entity (NME)

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Seroquel XR (quetiapine fumarate). FDA has determined that Seroquel XR (quetiapine fumarate) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Seroquel XR (quetiapine fumarate). FDA has determined that Seroquel XR (quetiapine fumarate) is a product for which patient

labeling could help prevent serious adverse effects and has serious risks (relative to benefits) of which patients should be made aware, because information concerning the risks could affect patients' decisions to use, or continue to use Seroquel XR (quetiapine fumarate).

The elements of the REMS will be a revised Medication Guide and a timetable for submission of assessments of the REMS.

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Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22047	SUPPL-11	ASTRAZENECA PHARMACEUTICA LS LP	SEROQUEL XR

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

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/s/

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JULIETTE T TOURE  
11/04/2009

THOMAS P LAUGHREN  
11/04/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-047/S-011**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22-047 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): SE-1  
10,11,12

Division Name: DPP PDUFA Goal Date: 12/27/08 Stamp Date: 2/27/2008

Proprietary Name: Seroquel XR

Established/Generic Name: quetiapine

Dosage Form: extended release tablets

Applicant/Sponsor: Astra Zeneca

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) Monotherapy and Adjunctive Therapy in the Treatment of Bipolar Mania in Adults

(2) Monotherapy in Treatment of Bipolar Depression in Adults

(3) Schizophrenia in Adults

(4) \_\_\_\_\_

---

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 3

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** 1) Monotherapy for Major Depressive Disorder; Adjunctive therapy for Major Depressive Disorder;  
3) Maintenance therapy for Major Depressive Disorder

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

Too few children with disease/condition to study

Other (e.g., patients geographically dispersed): \_\_\_\_\_

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input checked="" type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>0</u> yr. __ mo.	<u>6</u> yr. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): It is difficult to reliably diagnose Major Depressive Disorder in young children.

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	7 yr. __ mo.	17 yr. __ mo.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.**

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** adjunctive therapy in Major Depressive Disorder; 3) Maintenance therapy in Major Depressive Disorder (identical responses apply to each of the 3 indications in Major Depressive Disorder)**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input checked="" type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>0</u> yr. __ mo.	<u>6</u> yr. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): Major Depressive Disorder cannot be reliably diagnosed in young children.

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	7 yr. __ mo.	17 yr. __ mo.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

**This page was completed by:**

*{See appended electronic signature page}*

**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE **PEDIATRIC AND MATERNAL HEALTH STAFF** at **301-796-0700****

**(Revised: 6/2008)**

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

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Renmeet Grewal  
12/12/2008 10:35:40 AM

## EXCLUSIVITY SUMMARY

NDA # 22-047

SUPPL # 011

HFD # 130

Trade Name Seroquel XR Extended-Release tablets

Generic Name quetiapine fumarate

Applicant Name AstraZeneca Pharmaceuticals LP

Approval Date, If Known 12/2/2009

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1 (new indication - adjunctive treatment in MDD)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 22-047

Seroquel XR (quetiapine fumarate) extended-release tablet

NDA# 20-639

Seroquel (quetiapine fumarate) tablet

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

D1448C00006 and D1448C00007

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

D1448C00006 and D1448C00007

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 73,851      YES       !  
!      ! NO   
! Explain:

Investigation #2  
IND # 73,851      YES       !  
!      ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
YES       !  
!      ! NO   
Explain:      ! Explain:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Juliette Toure, PharmD  
Title: Senior Regulatory Project Manager  
Date: December 2, 2009

Name of Office/Division Director signing form: Thomas P. Laughren, MD  
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22047	SUPPL-11	ASTRAZENECA PHARMACEUTICA LS LP	SEROQUEL XR

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/s/

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JULIETTE T TOURE  
12/02/2009

THOMAS P LAUGHREN  
12/02/2009

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 022047 BLA #	NDA Supplement # 011 BLA STN #	If NDA, Efficacy Supplement Type: SE1 - new indication
Proprietary Name: Seroquel XR Established/Proper Name: quetiapine fumarate Dosage Form: Extended Release Tablets		Applicant: AstraZeneca Agent for Applicant (if applicable):
RPM: Juliette Toure, PharmD		Division: 130 Division of Psychiatry Products
<p><b>NDA:</b> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input type="checkbox"/> No changes      <input type="checkbox"/> Updated Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		12/2/2009
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input type="checkbox"/> None    CR - 12/22/2009
❖ Promotional Materials ( <i>accelerated approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics <sup>2</sup>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority          Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC</p> <p>Comments: _____</p>	
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: _____	November 12, 2008
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
<b>CONTENTS OF ACTION PACKAGE</b>	
❖ Copy of this Action Package Checklist <sup>3</sup>	December 2, 2009
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Approval December 2, 2009
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	November 23, 2009
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	June 2, 2009
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	November 23, 2009

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 8/26/09

<ul style="list-style-type: none"> <li>Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	November 24, 2009
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	June 2, 2009
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>	
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Review(s) (<i>indicate date(s)</i>)</li> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul>	
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM 10/22/2009 <input type="checkbox"/> DMEDP <input checked="" type="checkbox"/> DRISK 8/28/2009 <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	11/21/08 Filing Review
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP               <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatric Page ( <i>approvals only, must be reviewed by PERC before finalized</i> )	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>PeRC (<i>indicate date of mtg; approvals only</i>)</li> </ul>	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)</li> </ul>	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 8/26/09

<ul style="list-style-type: none"> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	4/7/2009 to 4/8/2009
<ul style="list-style-type: none"> <li>48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/2/09
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/21/09
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	10/21/09
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	8/10/09
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo (<i>indicate date</i>)</li> <li>Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	11/4/09 11/4/09 <input type="checkbox"/> None DRISK - MedGuide - 8/28/09
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 8/26/09

Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input type="checkbox"/> None
<b>Nonclinical</b>	<input checked="" type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input type="checkbox"/> None requested
<b>Product Quality</b>	<input checked="" type="checkbox"/> None
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• ONDQA Biopharmaceutics review <i>(indicate date for each review)</i>	
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
• BLAs: ○ TBP-EER	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) ( <i>date completed must be within 60 days prior to AP</i> )	Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22047

-----  
SUPPL-11

-----  
ASTRAZENECA  
PHARMACEUTICA  
LS LP

-----  
SEROQUEL XR

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

12/02/2009



NDA 020639/S-045/S-046  
NDA 022047 (b) (4) S-011 (b) (4)

## INFORMATION REQUEST

AstraZeneca Pharmaceuticals LP  
Attention: Pat Patterson  
Director, Regulatory Affairs  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Dear Ms. Patterson:

Please refer to your supplemental new drug applications dated and received on October 28, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Seroquel (quetiapine fumarate) 25 mg, 50 mg, 100 mg, 200 mg, 300 mg and 400 mg tablets.

We also refer to your supplemental new drug applications dated and received on February 27, 2008 for Seroquel XR (quetiapine fumarate) Extended-Release 50mg, 150mg, 200mg, 300mg, and 400mg Tablets.

FDA received a recent inquiry from a consumer who raised a general question of whether or not FDA has in its possession all the relevant safety data it needs to make final decisions about pending applications from several manufacturers whose products were involved in certain tort litigation. This consumer referred to pending tort litigation in New Jersey involving three atypical antipsychotic drugs, including Seroquel. Allegedly a 3-judge panel was appointed to give an opinion on whether the documents involved should be made publically available, and this panel presumably recommended that the documents be released. The consumer has alleged that the documents have remained sealed, however, because of an objection by one of the manufacturers involved in this case. The consumer has raised the question of whether or not FDA has access to any such sealed documents and has had an opportunity to examine them. The consumer has urged FDA to request these documents from the companies involved.

Under 505(k) of the FFDCFA, NDA holders are required to establish and maintain such records, and make such reports, "of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug," as FDA may require, "to determine, or facilitate a determination, whether there is or may be ground for" revoking approval. Additionally, under 21 CFR 314.80 and 314.81, when appropriate, NDA

holders must submit the following reports bearing on drug safety: (1) 15-day expedited reports; (2) periodic reports; (3) field alert reports; and (4) annual reports.

By this letter, we are asking you to ensure that you are in compliance with all applicable statutes and regulations, and we further request that you submit to the agency all data and information regarding any quetiapine products involved in the New Jersey case in question. If there were no documents or other information from your company that were involved in this litigation, we ask that you formally assert that by return letter. We would be happy to discuss these matters if you would find that helpful in preparing a response to this inquiry.

If you have any questions, call Kimberly Updegraff, M.S, Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20639	SUPPL-45	ASTRAZENECA LP	SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA-20639	SUPPL-46	ASTRAZENECA LP	SEROQUEL(QUETIAPINE FUMARATE)25/100/200M

(b) (4)

NDA-22047	SUPPL-11	ASTRAZENECA PHARMACEUTICALS LP	SEROQUEL XR
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(b) (4)

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

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THOMAS P LAUGHREN  
11/24/2009

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-047 Supplement # 010/ 011/ 012 Efficacy Supplement Type SE-

Proprietary Name: Seroquel XR  
Established Name: Quetiapine fumarate extended-release  
Strengths: 50mg, 200mg, 300mg, 400mg

Applicant: AstraZeneca Pharmaceuticals LP  
Agent for Applicant (if applicable): Gerald L. Limp

Date of Application: 2/27/08  
Date of Receipt: 2/27/08  
Date clock started after UN:  
Date of Filing Meeting: 4/9/08  
Filing Date: 5/7/08  
Action Goal Date (optional): User Fee Goal Date: 12/27/08

Indication(s) requested: Monotherapy, Adjunctive, and Maintenance treatment of Major Depressive Disorder

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.)  
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain: New Dosage Form Expires May 17, 2010

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO

- Exclusivity requested? YES, 3 Years NO

*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO

- Is this submission a partial or complete response to a pediatric Written Request? YES  NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**

*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO

- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. yes

- List referenced IND numbers: IND 32,132; IND 45,456; IND 73,851; IND 73,864, IND 76,146,

- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s) Date(s) \_\_\_\_\_ NO   
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) May 11, 2007 NO

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO

- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: 4-9-08

NDA #: 22-047

DRUG NAMES: Seroquel XR

APPLICANT: Astra Zeneca

BACKGROUND: This is an already approved drug and the sponsor is seeking an indication for treatment of monotherapy, adjunctive & maintenance therapy of Major Depressive Disorder (MDD)

ATTENDEES: Thomas Laughren,  
Mitchell Mathis  
Ni Khi  
Nallaperum Chidambaram  
Kofi Ansah  
Earl Hearst  
Philip Dinh  
Kofi Kumi  
Raman Baweja  
Peiling Yang

ASSIGNED REVIEWERS (including those not present at filing meeting) :

**Discipline/Organization**

**Reviewer**

Medical:	Earl Hearst
Secondary Medical:	Robert Levin
Statistical:	Philip Dinh
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	Julia Pinto/ Nallaperum Chidamberum
Environmental Assessment (if needed):	
Biopharmaceutical:	Kofi Kumi
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Diane Tesch
OPS:	
Regulatory Project Management:	Renmeet Grewal/ Kofi Ansah
Other Consults:	

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE

- Clinical site audit(s) needed? YES  NO   
If no, explain:
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?  
N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

- GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

- Establishment(s) ready for inspection? YES  NO
- Sterile product? YES  NO
- If yes, was microbiology consulted for validation of sterilization? YES  NO

**ELECTRONIC SUBMISSION:**

Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

---

Kofi Ansah, Pharm.D./ Renmeet Grewal, Pharm.D.  
Regulatory Project Manager/Senior Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): 20-639

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES  NO

*If "Yes," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product? YES  NO

*If "Yes "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO

*If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*

Pharmaceutical equivalent(s): Seroquel (Quetiapine fumarate) Immediate Release

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

*If “Yes,” to (c), proceed to question 7.*

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES  NO

*If “No,” skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is YES  NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES  NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES  NO

*If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A  YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

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Renmeet Grewal  
11/21/2008 02:09:50 PM  
CSO

**Toure, Juliette T**

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**From:** Toure, Juliette T  
**Sent:** Friday, November 20, 2009 2:56 PM  
**To:** 'Patterson, Pat'  
**Cc:** Vickers, Angela C  
**Subject:** Seroquel XR 022047 - REMS comments

**Importance:** High

**Attachments:** SERQUEL XR REMS - tracked changes.pdf

Dear Pat,

Please refer to your supplemental new drug applications, NDA 022047/S011. These applications provide for the use of Seroquel XR tablets for adjunctive therapy in the treatment of Major Depressive Disorder (MDD) and respective labeling changes.

We also refer to your submission dated and received on November 16, 2009 containing a response to our November 4, 2009 REMS Notification Letter requesting a REMS and REMS Supporting Document.

We have completed our review of your submission and have the following comments:

a. GOAL

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of SEROQUEL XR (quetiapine fumarate) Extended-Release Tablets.

b. Please see the attached document for comments related to the Medication Guide distribution plan for this proposed REMS.

c.  (b) (4)

-  (b) (4)

d. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable. Please see the attached document for comments related to this section of the proposed REMS.

e. We acknowledge your plan to conduct a survey of patients in the REMS Supporting Document. Please submit for review a detailed plan to evaluate patients' understanding about the safe use of SEROQUEL XR (quetiapine fumarate). This information does not need to be submitted for FDA review prior to approval of your REMS; however, it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS Correspondence." If you plan to conduct this assessment using a survey, your submission should include:

- All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of SEROQUEL XR (quetiapine fumarate). This should include, but not be limited

to:

- Sample size and confidence associated with that sample size
  - How the sample will be determined (selection criteria)
  - The expected number of patients to be surveyed
  - How the participants will be recruited
  - How and how often the surveys will be administered
  - Explain controls used to minimize bias
  - Explain controls used to compensate for the limitations associated with the methodology
- The survey instruments (questionnaires and/or moderator's guide).
  - Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Please note that the attached a copy of the REMS proposal for SEROQUEL XR (quetiapine fumarate) contains tracked changes corresponding to comments above.

Please respond to our comments by COB on Tuesday, November 24, 2009. If you are unable to respond by the requested time, please let us know as soon as possible.



SEROQUEL XR REMS  
- tracked chan...

Best regards,  
Juliette

Juliette Touré, PharmD  
LCDR, United States Public Health Service  
Senior Regulatory Project Manager  
U.S. Food and Drug Administration  
Division of Psychiatry Products  
(301) 796-5419

2 Pages Immediately Following Withheld - b(4)

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22047

-----  
SUPPL-11

-----  
ASTRAZENECA  
PHARMACEUTICA  
LS LP

-----  
SEROQUEL XR

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/s/  
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JULIETTE T TOURE

11/20/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Division/Office): Office of Surveillance and Epidemiology / Division of Risk Management (DRISK)  Abolade Adeolu (OSE Project Manager)			FROM: HFD-130/ Division of Psychiatry Products		
DATE 07/21/2009	IND NO.	NDA NO. 22-047 (b) (4) 011 (b) (4)	TYPE OF DOCUMENT	DATE OF DOCUMENT 2 Jun 2009	
NAME OF DRUG Seroquel XR (quetiapine fumarate)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Major Depressive Disorder	DESIRED COMPLETION DATE 2 Sep 2009	
NAME OF FIRM: AstraZeneca Pharmaceuticals, LP					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	
<b>II. BIOMETRICS</b>					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> The sponsor submitted a (b) (4) response to an CR letter DPP sent to Astra Zeneca asking for a comprehensive medication guide. The sponsor has responded with a comprehensive medication guide. Please review the attached comprehensive medication guide and let me know if you have any comments or recommendations to convey to the sponsor.					
SIGNATURE OF REQUESTER Juliette Touré, Pharm.D. Senior Regulatory Project Manager 301-796-5419 Juliette.Toure@fda.hhs.gov			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

10 Pages Immediately Following Withheld - b(4) Draft Labeling

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
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(b) (4)

NDA 22047	SUPPL 11	ASTRAZENECA PHARMACEUTICA LS LP	SEROQUEL XR
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/s/

RENMEET K GREWAL on behalf of JULIETTE T TOURE  
07/27/2009

THOMAS P LAUGHREN  
07/27/2009



NDA 022047 (b) (4) S-011 (b) (4)

**ACKNOWLEDGEMENT CLASS 2 RESPONSE**

AstraZeneca  
Attention: Susanne Fors  
Senior Regulatory Affairs Director  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Dear Ms. Fors:

We acknowledge receipt on 2 June 2009 of your 2 June 2009 resubmission to your supplemental new drug application for Seroquel XR (quetiapine fumarate) Extended-Release Tablets 50mg, 150mg, 200mg, 300mg, and 400mg.

We consider this a (b) (4), class 2 response to our 22 December 2008 action letter. Therefore, the user fee goal date is 2 December 2009.

If you have any questions, email me at [Juliette.Toure@fda.hhs.gov](mailto:Juliette.Toure@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Juliette Touré, Pharm.D.  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

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/s/

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Juliette Toure

7/17/2009 09:47:08 AM

# DSI CONSULT: Request for Clinical Inspections

**Date:**

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46  
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47  
Name of DSI Primary Reviewer (if known)

**Through:** Earl Hearst, M.D./Division of Psychiatry Products/HFD-130  
Robert Levin, M.D., (CDTL) and Tom Laughren, M.D (Director)  
Division of Psychiatry Products /HFD-130

**From:** LCDR Kofi Ansah, Regulatory Health Project Manager  
Division of Psychiatry Products /HFD-130

**Subject:** Request for Clinical Site Inspections

## **I. General Information**

Application#: NDA-22047/SE1-010/SE1-011/SE1-012

Sponsor/Sponsor contact information (to include phone/email):

AstraZeneca Pharmaceuticals LP  
Attention: Gerald Limp  
Director, Regulatory Affairs  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Drug: Seroquel XR (quetiapine fumarate extended-release)

NME: No

Standard or Priority: Standard

Study Population < 18 years of age: No

Pediatric exclusivity:

PDUFA:

Action Goal Date: December 27, 2008

Inspection Summary Goal Date: August 27, 2008

## **II. Background Information**

This is a supplement for a new indication

Proposed indication: Treatment for Monotherapy of Major Depressive Disorder (MDD), Treatment of Adjunctive Therapy of MDD, Treatment of Maintenance Therapy of MDD

**III. Protocol/Site Identification**

Investigator	Site	Study number	Site number (# of subjects)
Linda Harper (PI) (b) (6)	Clinical Neurosciences Solutions, Inc. 77 W. Underwood Street, 3 <sup>rd</sup> Floor Orlando, FL 32806	D1448C00002	1013 55 subjects
Miguel Flores (b) (6)	Berma Research Group 7150 West 20 <sup>th</sup> Avenue Suite 515 Hialeah, FL 33016	D1448C00005	1037 18 subjects
Ronald Brenner (PI) (b) (6)	Neurobehavioral Research Inc 74 Carman Ave Cedarhurst, NY 11516	D1448C00006	1019 29 subjects

**IV. Site Selection/Rationale**

We have selected the largest study for each of the three new indications. There are no specific statistical or clinical concerns.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

Page 3-Request for Clinical Inspections

Should you require any additional information, please contact *LCDR Kofi Ansah* at Ph: 301-796-4158 or *Earl Hearst* at Ph: 301-796-1087.

Concurrence: (as needed)

\_\_\_\_\_ Medical Team Leader  
\_\_\_\_\_ Medical Reviewer  
\_\_\_\_\_ Director, Division Director (for foreign inspection requests  
only)

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/s/

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Thomas Laughren  
5/15/2008 08:32:09 AM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-047/S-010/S-011/S-012

AstraZeneca Pharmaceuticals LP  
Attention: Gerald Limp  
Director, Regulatory Affairs  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Dear Mr. Limp:

We acknowledge receipt of your supplemental new drug applications dated February 27, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel XR (quetiapine fumarate) extended-release 50mg, 200mg, 300mg, and 400mg tablets.

These supplemental applications propose the following changes: new indication for the treatment of major depressive disorder (monotherapy, adjunctive, and maintenance).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, these applications have been filed under section 505(b) of the Act on April 27, 2008 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We have additionally determined that these applications qualify for a standard review priority classification. Therefore, the user fee goal date will be December 27, 2008.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Psychiatry Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call LCDR Kofi Ansah, Regulatory Project Manager, at (301) 796-4158.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.

Director

Division of Psychiatry Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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/s/

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Thomas Laughren  
5/7/2008 12:46:56 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Division/Office): <b>HFD- 710/Stat</b> Attention: Peiling Yang			FROM: <b>HFD-130/ Division of Psychiatry Products</b>		
DATE 3/14/08	IND NO.	NDA NO. sNDA 22-047 010,011,012	TYPE OF DOCUMENT New supplements for 3 new indications	DATE OF DOCUMENT February 27,2008	
NAME OF DRUG  Seroquel XR		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE <b>Filing meting: 4/9/08</b> <b>PDUFA date: 12/27/08</b>	
NAME OF FIRM: <i>Astra Zeneca</i>					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	
<b>II. BIOMETRICS</b>					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: These are new supplements for Seroquel XR. The supplements are as follows: NDA 22-047/S-010 Treatment for Monotherapy of MDD, NDA 22-047/S-011 Treatment for Adjunctive Therapy of MDD, NDA 22-047/S-012 Treatment for Maintenance Therapy of MDD. The link to the supplemental NDA is <a href="\\CDSESUB1\EVSPROD\NDA022047\022047.enx">\\CDSESUB1\EVSPROD\NDA022047\022047.enx</a> The <b>Filing meeting is on 4/9/08</b> and the <b>PDUFA date is 12/27/08</b> . Thanks, Rimmy					
SIGNATURE OF REQUESTER Renmeet Grewal Pharm.D. Regulatory Project Manager 301-796-1080 grewalr@fda.hhs.gov			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

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Renmeet Grewal  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>HFD- 860/Biopharm</b> Attention: Raman Baweja		FROM: HFD-130/ Division of Psychiatry Products		
DATE 3/6/08	IND NO.	NDA NO. sNDA 22-047 010,011,012	TYPE OF DOCUMENT New supplements for 3 new indications	DATE OF DOCUMENT February 27,2008
NAME OF DRUG Seroquel XR		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE <b>Filing meting: 4/9/08</b> <b>PDUFA date: 12/27/08</b>
NAME OF FIRM: <b>Astra Zeneca</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:  These are new supplements for Seroquel XR. The supplements are as follows: NDA 22-047/S-010 Treatment for Monotherapy of MDD, NDA 22-047/S-011 Treatment for Adjunctive Therapy of MDD, NDA 22-047/S-012 Treatment for Maintenance Therapy of MDD. The <b>Filing meeting is on 4/9/08</b> and the <b>PDUFA date is 12/27/08</b> . Thanks, Rimmy				
SIGNATURE OF REQUESTER <b>Renmeet Grewal Pharm.D.</b> Regulatory Project Manager 301-796-1080 grewalr@.fda.hhs.gov		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
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## MEMORANDUM OF TELECON

DATE: January 23, 2009

APPLICATION NUMBER: NDA 22-047/S-010/S-011/S-012/S-014/S-015

**BETWEEN:**

Name: Hans Eriksson - Seroquel Medical Science Director  
Ihor Rak - Clinical Vice President - Neuroscience  
Willie Earley - Seroquel MDD Physician  
Ron Leong - Patient Safety Executive Director  
[REDACTED] (b) (6)  
John Ramsey - Seroquel Vice President Development  
Mark Scott - US Seroquel Executive Director Development  
Gary Horowitz - US Regulatory Affairs Executive Director - Neuroscience  
Susanne Fors - Seroquel Global Regulatory Affairs Director  
Duncan Nickless - Seroquel Global Regulatory Affairs Associate Director  
Pat Patterson - Seroquel Global Regulatory Affairs Associate Director

Phone: 1-866-222-5320 Code: 8630688

Representing: AstraZeneca

**AND**

Name: Division of Psychiatry Products, HFD-130, FDA  
Thomas Laughren, Division Director  
Mitchell Mathis, M.D., Deputy Director  
Ni Khin, M.D., Medical Team Leader  
Robert Levin, M.D., Medical Team Leader  
Ripi-Kavneet Kohli-Chhabra, M.D., Medical Reviewer  
Renmeet Grewal, Senior Regulatory Project Manager

**SUBJECT:** Discussion of upcoming Psychiatric Drug Advisory Committee (PDAC) meeting for Seroquel XR for the treatment of MDD & GAD

The division discussed the objectives of the PDAC meeting with AstraZeneca. The sponsor was informed that the division has several goals for this meeting:

1. A general presentation of efficacy and safety of 2 new indications.
2. In addition, the meeting will focus on certain specific potential longer-term risks associated with the expanded use of this drug into a non-psychotic population (MDD, GAD).
  - Metabolic issues - consideration of a possible longer-term burden of metabolic effects
  - Tardive Dyskenisa (TD) - consideration of a possible longer-term of tardive

- dyskinesia.
- Sudden Cardiac Death - discussion of the recent publication by Wayne Ray et. al. in NEJM

Thus, it was suggested that the sponsor should provide background materials that address these concerns. They might consider looking at larger databases, e.g., the VA. The agency agrees that AIMS test results would be acceptable.

FDA will likely make a presentation regarding the metabolic issue based on our review of the sponsor's June 2008 submission. The Division has requested that members of the Psychopharmacology Committee will be in attendance along with special government employees (SGE) with expertise in cardiology and endocrinology.

The sponsor proposed Risk Minimization Activities such as labeling changes (baseline lipid & weight monitoring), changing the Medguide (b) (4) and enhanced educational activities for prescribers.

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LCDR Renmeet Grewal, Pharm.D  
Senior Regulatory Project Manager

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