

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### ***APPLICATION NUMBER:***

**020639Orig1s046**

***Trade Name:*** SEROQUEL

***Generic or Proper Name:*** Quetiapine fumarate

***Sponsor:*** AstraZeneca

***Approval Date:*** December 02, 2009

***Indication:***

SEROQUEL is an atypical antipsychotic indicated for the:

Treatment of schizophrenia (1.1)

- Adults: Efficacy was established in three 6-week clinical trials in patients with schizophrenia (14.1)
- Adolescents (ages 13-17): Efficacy was established in one 6-week trial in patients with schizophrenia (14.1)

Acute treatment of manic episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex (1.2)

- Adults: Efficacy was established in two 12-week monotherapy trials and in one 3-week adjunctive trial in patients with manic episodes associated with bipolar I disorder (14.2)
- Children and adolescents (ages 10-17): Efficacy was established in one 3-week monotherapy trial in patients with manic episodes associated with bipolar I disorder (14.2)

Acute treatment of depressive episodes associated with bipolar disorder (1.2)

- Adults: Efficacy was established in two 8-week trials in patients with bipolar I or II disorder (14.2) Maintenance treatment of bipolar disorder as an adjunct to lithium or divalproex (1.2).

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 020639Orig1s046

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**020639Orig1s046**

**APPROVAL LETTER**



NDA 020639/S-045/S-046

**SUPPLEMENT APPROVAL**

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 (sNDAs) 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 acknowledge receipt of your submissions dated:

October 30, 2008	November 5, 2008	December 22, 2008	February 17, 2009
February 27, 2009	March 17, 2009	March 19, 2009	May 5, 2009
June 16, 2009	July 2, 2009	October 22, 2009	

These supplemental new drug applications provide for the use of Seroquel (quetiapine fumarate) tablets for the treatment of schizophrenia in adolescents 13 to 17 years of age and the treatment of bipolar mania in children and adolescents 10 to 17 years of age.

We have completed our review of these applications. They are 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 (b)(4), September 11, 2008 (b)(4), December 4, 2008 (b)(4) and your “Prior Approval” supplement submitted on July 19, 2007 (b)(4) have been superseded by this approval action. Therefore, 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 and Medication Guide). For administrative purposes, please designate this submission, "SPL for approved NDA 020639/S-045/S-046.

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.

### **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 (quetiapine fumarate) was approved on September 26, 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 (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 October 22, 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 (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 020639 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 020639  
PROPOSED REMS MODIFICATION  
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 020639  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

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

**PROMOTIONAL MATERIALS**

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

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

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. 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 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

Enclosures

Content of Labeling

REMS

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

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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  
RESEARCH**

*APPLICATION NUMBER:*

**020639Orig1s046**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use SEROQUEL safely and effectively. See full prescribing information for SEROQUEL. **SEROQUEL (quetiapine fumarate) Tablets**  
Initial US 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 Psychosis (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-----

Boxed Warning: Suicidality and Antidepressant Drugs, (11/2009)  
Indications and Usage, Schizophrenia (1.1), 11/2009  
Indications and Usage, Bipolar Mania (1.2), 11/2009  
Indications and Usage, Special Considerations in Treating Pediatric Patients with Schizophrenia and Bipolar I Disorder (1.3), 11/2009  
Dosage and Administration, Schizophrenia, Adolescents (2.1), 11/2009  
Dosage and Administration, Bipolar Mania, Children and Adolescents (2.2), 11/2009  
Warnings and Precautions, Hyperglycemia (5.4), 11/2009  
Warnings and Precautions, Hyperlipidemia (5.5), 11/2009  
Warnings and Precautions, Weight Gain (5.6), 11/2009  
Warnings and Precautions, Increases in Blood Pressure in Children and Adolescents (5.9), 11/2009  
Warnings and Precautions, Hypothyroidism (5.13), 01/2009  
Warnings and Precautions, Hyperprolactinemia (5.14), 01/2009

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

SEROQUEL is an atypical antipsychotic indicated for the:  
Treatment of schizophrenia (1.1)

- Adults: Efficacy was established in three 6-week clinical trials in patients with schizophrenia (14.1)
- Adolescents (ages 13-17): Efficacy was established in one 6-week trial in patients with schizophrenia (14.1)

Acute treatment of manic episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex (1.2)

- Adults: Efficacy was established in two 12-week monotherapy trials and in one 3-week adjunctive trial in patients with manic episodes associated with bipolar I disorder (14.2)
- Children and adolescents (ages 10-17): Efficacy was established in one 3-week monotherapy trial in patients with manic episodes associated with bipolar I disorder (14.2)

Acute treatment of depressive episodes associated with bipolar disorder (1.2)

- Adults: Efficacy was established in two 8-week trials in patients with bipolar I or II disorder (14.2)

Maintenance treatment of bipolar disorder as an adjunct to lithium or divalproex (1.2)

- Adults: Efficacy was established in two maintenance trials in adults (14.2)

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

SEROQUEL can be taken with or without food.

Indication	Dosing Instructions*	Recommended Dose / Dose Range
Schizophrenia-Adults (2.1)	Day 1: 25 mg twice daily. Increase in increments of 25 mg-50 mg divided two or three times on Days 2 and 3 to range of 300-400 mg by Day 4. Further adjustments can be made in increments of 25-50 mg twice a day, in intervals of not less than 2 days.	150-750 mg/day
Schizophrenia-Adolescents (13-17 years) (2.1)	Day 1: 25 mg twice daily. Day 2: Twice daily dosing totaling 100 mg. Day 3: Twice daily dosing totaling 200	400-800 mg/day

	mg Day 4: Twice daily dosing totaling 300 mg. Day 5: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-800 mg/day. Based on response and tolerability, may be administered three times daily.	
Bipolar Mania-Adults Monotherapy or as an adjunct to lithium or divalproex (2.2)	Day 1: Twice daily dosing totaling 100 mg. Day 2: Twice daily dosing totaling 200 mg. Day 3: Twice daily dosing totaling 300 mg Day 4: Twice daily dosing totaling 400 mg.  Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day	400- 800 mg/day
Bipolar Mania-Children and Adolescents (10 to 17 years), Monotherapy	Day 1: 25 mg twice daily. Day 2: Twice daily dosing totaling 100mg. Day 3: Twice daily dosing totaling 200 mg Day 4: Twice daily dosing totaling 300 mg. Day 5: Twice daily dosing totaling 400 mg.  Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-600 mg/day. Based on response and tolerability, may be administered three times daily.	400-600 mg/day
Bipolar Depression-Adults	Administer once daily at bedtime Day 1: 50 mg Day 2: 100mg Day 3: 200 mg Day 4: 300 mg	300 mg/day
Bipolar I Disorder Maintenance Therapy- Adults	Administer twice daily totaling 400-800 mg/day as adjunct to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized.	

\*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

25 mg, 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg (3)

-----CONTRAINDICATIONS-----

None (4)

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

- **Increased Mortality in Elderly Patients with Dementia-Related Psychoses:** Atypical 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. (5.3)

• **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. (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 (5.9)

• **Leukopenia, Neutropenia and Agranulocytosis** have been reported with atypical antipsychotics including SEROQUEL. 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 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-----

Most common adverse reactions (incidence  $\geq$ 5% and twice placebo):

Adults: somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, weight gain, lethargy, ALT increased, dyspepsia. (6.1)

Children and Adolescents: somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, weight increased (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. (8.5)

• **Hepatic Impairment:** Lower starting doses (25 mg/day) and slower titration may be needed. (2.3, 12.3)

• **Pregnancy and Nursing Mothers:** Quetiapine should be used only if the potential benefit justifies the potential risk. (8.1) Breastfeeding is not recommended. (8.3)

• **Pediatric Use:** Safety and effectiveness has only been established for schizophrenia in adolescent patients 13 to 17 years of age and in bipolar mania in children and adolescent patients 10 to 17 years of age (8.4).

-----SEE 17 FOR PATIENT COUNSELING INFORMATION

Revised 11/2009

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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. 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 (quetiapine) 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 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 is not approved for use in patients under ten years of age [see *Warnings and Precautions* (5.2)].

# 1 INDICATIONS AND USAGE

## 1.1 Schizophrenia

SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in three 6-week trials in adults and one 6-week trial in adolescents (13-17 years). The effectiveness of SEROQUEL for the maintenance treatment of schizophrenia has not been systematically evaluated in controlled clinical trials. [*see Clinical Studies (14.1)*].

## 1.2 Bipolar Disorder

SEROQUEL is indicated for the acute treatment of manic episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex. Efficacy was established in two 12-week monotherapy trials in adults, in one 3-week adjunctive trial in adults, and in one 3-week monotherapy trial in pediatric patients (10-17 years). [*see Clinical Studies (14.2)*].

SEROQUEL is indicated as monotherapy for the acute treatment of depressive episodes associated with bipolar disorder. Efficacy was established in two 8-week monotherapy trials in adult patients with bipolar I and bipolar II disorder [*see Clinical Studies (14.2)*].

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

## 1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder

Pediatric schizophrenia and bipolar I disorder are serious mental disorders, however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder is indicated as part of a total treatment program that

often includes psychological, educational and social interventions.

## **2 DOSAGE AND ADMINISTRATION**

SEROQUEL can be taken with or without food

### **2.1 Schizophrenia**

#### **Adults**

Dose Selection—SEROQUEL should generally be administered with an initial dose of 25 mg twice daily, with increases in total daily dose of 25 mg - 50 mg divided in two or three doses on the second and third day, as tolerated, to a total dose range of 300 mg to 400 mg daily by the fourth day. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state for SEROQUEL would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25mg - 50 mg divided twice daily are recommended. Most efficacy data with SEROQUEL were obtained using three times daily dosing regimens, but in one controlled trial 225 mg given twice per day was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 mg/day to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400 mg/day - 500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Maintenance Treatment—The effectiveness of SEROQUEL for longer than 6 weeks has not been evaluated in controlled clinical trials. While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should be maintained, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

#### **Adolescents (13-17 years)**

Dose Selection—SEROQUEL should be administered twice daily. However, based on response and tolerability

SEROQUEL may be administered three times daily where needed.

The total daily dose for the initial five days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4) and 400 mg (Day 5). After day 5, the dose should be adjusted within the recommended dose range of 400 mg/day to 800 mg/day based on response and tolerability. Dosage adjustments should be in increments of no greater than 100 mg/day. Efficacy was demonstrated with SEROQUEL at both 400 mg and 800 mg; however, no additional benefit was seen in the 800 mg group.

Maintenance Treatment—The effectiveness of SEROQUEL for longer than 6 weeks has not been evaluated in controlled clinical trials. While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should be maintained, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

## 2.2 Bipolar Disorder

### Adults

#### Acute Treatment of Manic Episodes in Bipolar I Disorder

Dose Selection—When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL should be initiated in twice daily doses totaling 100 mg/day on Day 1, increased to 400 mg/day on Day 4 in increments of up to 100 mg/day in twice daily divided doses. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. Data indicate that the majority of patients responded between 400 mg/day to 800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

#### Acute Treatment of Depressive Episodes in Bipolar Disorder

Dose Selection—SEROQUEL should be administered once daily at bedtime to reach 300 mg/day by Day 4.

#### Recommended Dosing Schedule

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

In these clinical trials supporting effectiveness, the dosing schedule was 50 mg, 100 mg, 200 mg and 300 mg/day for Days 1-4 respectively. Patients receiving 600 mg increased to 400 mg on Day 5 and 600 mg on Day 8 (Week 1). Antidepressant efficacy was demonstrated with SEROQUEL at both 300 mg and 600 mg; however, no additional benefit was seen in the 600 mg group.

### **Maintenance Treatment of Bipolar I Disorder**

Maintenance of efficacy in bipolar I disorder was demonstrated with SEROQUEL (administered twice daily totaling 400 to 800 mg per 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 [*see Clinical Studies (14.2)*].

### **Children and Adolescents (10 to 17 years)**

#### Acute Treatment of Manic Episodes in Bipolar I Disorder

Dose Selection—SEROQUEL should be administered twice daily. However, based on response and tolerability SEROQUEL may be administered three times daily where needed.

The total daily dose for the initial five days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4) and 400 mg (Day 5). After day 5, the dose should be adjusted within the recommended dose range of 400 to 600 mg/day based on response and tolerability. Dosage adjustments should be in increments of no greater than 100 mg/day. Efficacy was demonstrated with SEROQUEL at both 400 mg and 600 mg; however, no additional benefit was seen in the 600 mg group.

#### Maintenance Treatment of Bipolar I Disorder

The effectiveness of SEROQUEL for longer than 3 weeks has not been evaluated in controlled clinical trials of children and adolescents. While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should be maintained, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

## 2.3 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 *Clinical Pharmacology* (12)]. When indicated, dose escalation should be performed with caution in these patients.

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25 mg/day - 50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

#### 2.4 Reinitiation of Treatment in Patients Previously Discontinued

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

#### 2.5 Switching from Antipsychotics

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

### 3 DOSAGE FORMS AND STRENGTHS

25 mg tablets  
50 mg tablets  
100 mg tablets  
200 mg tablets  
300 mg tablets  
400 mg tablets

## 4 CONTRAINDICATIONS

None known

## 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. SEROQUEL (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 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. It should be noted that SEROQUEL is approved for use in treating adult bipolar 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 SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. 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 (e.g., 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 (e.g., 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.

*Adults:*

**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	Quetiapine	2907	71 (2.4%)
	(<100 mg/dL to $\geq 126$ mg/dL)	Placebo	1346	19 (1.4%)
	Borderline to High	Quetiapine	572	67 (11.7%)
	( $\geq 100$ mg/dL and <126 mg/dL) to $\geq 126$ mg/dL	Placebo	279	33 (11.8%)

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 SEROQUEL 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).

*Children and Adolescents:*

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 (≥100 mg/dL and <126 mg/dL) had a treatment-emergent blood glucose level of ≥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 3 shows the percentage of adult patients with changes in total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol from baseline by indication in clinical trials with SEROQUEL

**Table 3: Percentage of Adult Patients with Shifts in Total Cholesterol, Triglycerides, LDL-cholesterol and HDL-cholesterol from Baseline to Clinically Significant Levels by Indication**

Laboratory Analyte	Indication	Treatment Arm	N	Patients n (%)
Total Cholesterol $\geq$ 240 mg/dL	Schizophrenia <sup>a</sup>	Quetiapine	137	24 (18%)
		Placebo	92	6 (7%)
	Bipolar Depression <sup>b</sup>	Quetiapine	463	41 (9%)
		Placebo	250	15 (6%)
Triglycerides $\geq$ 200 mg/dL	Schizophrenia <sup>a</sup>	Quetiapine	120	26 (22%)
		Placebo	70	11 (16%)
	Bipolar Depression <sup>b</sup>	Quetiapine	436	59 (14%)
		Placebo	232	20 (9%)
LDL-Cholesterol $\geq$ 160 mg/dL	Schizophrenia <sup>a</sup>	Quetiapine	na <sup>c</sup>	na <sup>c</sup>
		Placebo	na <sup>c</sup>	na <sup>c</sup>
	Bipolar Depression <sup>b</sup>	Quetiapine	465	29 (6%)
		Placebo	256	12 (5%)
HDL-Cholesterol $\leq$ 40 mg/dL	Schizophrenia <sup>a</sup>	Quetiapine	na <sup>c</sup>	na <sup>c</sup>
		Placebo	na <sup>c</sup>	na <sup>c</sup>
	Bipolar Depression <sup>b</sup>	Quetiapine	393	56 (14%)
		Placebo	214	29 (14%)

a: 6 weeks duration

b: 8 weeks duration

c: Parameters not measured in the SEROQUEL registration studies for schizophrenia. Lipid parameters also were not measured in the bipolar mania registration studies.

*Children and Adolescents:* Table 4 shows the percentage of children and adolescents with changes in total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol from baseline in clinical trials with SEROQUEL.

**Table 4: Percentage of Children and Adolescents with Shifts in Total Cholesterol, Triglycerides, LDL-Cholesterol and HDL-Cholesterol from Baseline to Clinically Significant Levels**

<b>Laboratory Analyte</b>	<b>Indication</b>	<b>Treatment Arm</b>	<b>N</b>	<b>Patients n (%)</b>
Total Cholesterol ≥200 mg/dL	Schizophrenia <sup>a</sup>	Quetiapine	107	13 (12%)
		Placebo	56	1 (2%)
	Bipolar Mania <sup>b</sup>	Quetiapine	159	16 (10%)
		Placebo	66	2 (3%)
Triglycerides ≥150 mg/dL	Schizophrenia <sup>a</sup>	Quetiapine	103	17 (17%)
		Placebo	51	4 (8%)
	Bipolar Mania <sup>b</sup>	Quetiapine	149	32 (22%)
		Placebo	60	8 (13%)
LDL-Cholesterol ≥ 130 mg/dL	Schizophrenia <sup>a</sup>	Quetiapine	112	4 (4%)
		Placebo	60	1 (2%)
	Bipolar Mania <sup>b</sup>	Quetiapine	169	13 (8%)
		Placebo	74	4 (5%)
HDL-Cholesterol ≤ 40 mg/dL	Schizophrenia <sup>a</sup>	Quetiapine	104	16 (15%)
		Placebo	54	10 (19%)
	Bipolar Mania <sup>b</sup>	Quetiapine	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:** In clinical trials with SEROQUEL the following increases in weight have been reported.

**Table 5: Proportion of Patients with Weight Gain  $\geq 7\%$  of Body Weight (Adults)**

Vital sign	Indication	Treatment Arm	N	Patients n (%)
Weight Gain	Schizophrenia <sup>a</sup>	SEROQUEL	391	89 (23%)
		Placebo	206	11 (6%)
	Bipolar Mania (monotherapy) <sup>b</sup>	SEROQUEL	209	44 (21%)
		Placebo	198	13 (7%)
	Bipolar Mania (adjunct therapy) <sup>c</sup>	SEROQUEL	196	25 (13%)
		Placebo	203	8 (4%)
	Bipolar Depression <sup>d</sup>	SEROQUEL	554	47 (8%)
		Placebo	295	7 (2%)

a: up to 6 weeks duration

b: up to 12 weeks duration

c: up to 3 weeks duration

d: up to 8 weeks duration

**Children and Adolescents:** In two clinical trials with SEROQUEL, one in bipolar mania and one in schizophrenia, reported increases in weight are included in the table below.

**Table 6: Proportion of Patients with Weight Gain  $\geq 7\%$  of Body Weight (Children and Adolescents)**

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 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, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL 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 1% (28/3265) of the patients treated with SEROQUEL, compared with 0.2% (2/954) on placebo and about 0.4% (2/527) on active control drugs. Orthostatic hypotension, dizziness, and syncope may lead to falls.

SEROQUEL 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)*]. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg twice daily [*see Dosage and Administration (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 in Children and Adolescents

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 SEROQUEL. 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 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 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 Nonclinical Toxicology, Animal Toxicology* (13.2)]. Lens changes have also been observed in adults, children and adolescents during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL 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 clinical trials, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics, SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, eg, 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:* 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 thyroid stimulating hormone (TSH) was unchanged in most patients and levels of thyroid binding globulin (TBG) were unchanged. In nearly all cases, cessation of SEROQUEL 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 the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproex, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo-treated patients had elevated TSH levels. Of the SEROQUEL treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels.

*Children and Adolescents:* 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, 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:** 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 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. 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. In acute bipolar mania 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 12-week placebo-controlled trials were approximately 1% for both SEROQUEL (3/560) and placebo (3/294). 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 SEROQUEL. In bipolar depression trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in two 8-week placebo-controlled trials was 1% (5/698) for SEROQUEL and 2% (6/347) for placebo.

#### 5.16 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% (89/510) of patients on SEROQUEL compared to 11% (22/206) of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% (34/209) of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% (66/196) of patients on SEROQUEL compared to 9% (19/203) of placebo patients. In bipolar depression trials, somnolence was reported in 57% (398/698) of patients on SEROQUEL compared to 15% (51/347) of placebo patients. Since SEROQUEL 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 SEROQUEL therapy does not affect them adversely. Somnolence may lead to falls.

#### 5.17 Priapism

One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal

relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention.

#### 5.18 Body Temperature Regulation

Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., 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 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 bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

In 2 eight-week clinical studies in patients with bipolar depression (N=1048), the incidence of treatment emergent suicidal ideation or suicide attempt was low and similar to placebo (SEROQUEL 300 mg, 6/350, 1.7%; SEROQUEL 600 mg, 9/348, 2.6%; Placebo, 7/347, 2.0%).

#### 5.21 Use in Patients with Concomitant Illness

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

SEROQUEL 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, 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 SEROQUEL. Gradual withdrawal is advised.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Study Experience

#### Adults

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 consisting of over 4300 patients. This database includes 698 patients exposed to SEROQUEL for the treatment of bipolar depression, 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy), 646 patients exposed to SEROQUEL for the maintenance treatment of bipolar I disorder as adjunct therapy, and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia.

Of these approximately 4300 subjects, approximately 4000 (2300 in schizophrenia, 405 in acute bipolar mania, 698 in bipolar depression, and 646 for the maintenance treatment of bipolar I disorder) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 2400 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

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 reaction categories.

In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse reactions for schizophrenia and bipolar mania. MedDRA terminology has been used to classify reported adverse reactions for bipolar depression.

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. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

### **Incidence of Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adults**

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

*Schizophrenia:* Overall, there was little difference in the incidence of discontinuation due to adverse reactions (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence (0.8% SEROQUEL vs. 0% placebo) and hypotension (0.4% SEROQUEL vs. 0% placebo) were considered to be drug related [see *Warnings and Precautions* (5.8 and 5.16)].

*Bipolar Disorder:*

*Mania:* Overall, discontinuations due to adverse reactions were 5.7% for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy.

*Depression:* Overall, discontinuations due to adverse reactions were 12.3% for SEROQUEL 300 mg vs. 19.0% for SEROQUEL 600 mg and 5.2% for placebo.

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

In the acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) trials, the most commonly observed adverse reactions associated with the use of SEROQUEL monotherapy (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of

placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), ALT increased (5%), weight gain (5%), and dyspepsia (5%).

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

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

Table 7 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

**Table 7. Treatment-Emergent Adverse Reaction Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (Monotherapy)<sup>1</sup>**

<b>Body System/ Preferred Term</b>	<b>SEROQUEL (n=719)</b>	<b>PLACEBO (n=404)</b>
<b>Body as a Whole</b>		
Headache	21%	14%
Pain	7%	5%
Asthenia	5%	3%
Abdominal Pain	4%	1%
Back Pain	3%	1%
Fever	2%	1%
<b>Cardiovascular</b>		
Tachycardia	6%	4%
Postural	4%	1%

Hypotension

**Digestive**

Dry Mouth	9%	3%
Constipation	8%	3%
Vomiting	6%	5%
Dyspepsia	5%	1%
Gastroenteritis	2%	0%
Gamma Glutamyl Transpeptidase Increased	1%	0%

**Metabolic and  
Nutritional**

Weight Gain	5%	1%
ALT Increased	5%	1%
AST Increased	3%	1%

**Nervous**

Agitation	20%	17%
Somnolence	18%	8%
Dizziness	11%	5%
Anxiety	4%	3%

**Respiratory**

Pharyngitis	4%	3%
Rhinitis	3%	1%

**Skin and  
Appendages**

Rash	4%	2%
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**Special Senses**

Amblyopia	2%	1%
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<sup>1</sup> Reactions for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.

In the acute adjunct therapy of bipolar mania (up to 3 weeks) studies, the most commonly observed adverse reactions associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%),

postural hypotension (7%), pharyngitis (6%), and weight gain (6%).

Table 8 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 3 weeks) of acute mania in 1% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

**Table 8. Treatment-Emergent Adverse Reaction Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy)<sup>1</sup>**

<b>Body System/ Preferred Term</b>	<b>SEROQUEL (n=196)</b>	<b>PLACEBO (n=203)</b>
<b>Body as a Whole</b>		
Headache	17%	13%
Asthenia	10%	4%
Abdominal Pain	7%	3%
Back Pain	5%	3%
Hormone Level Altered	3%	0%
Heaviness	2%	1%
Infection	2%	1%
Fever	2%	1%
Neck Rigidity	1%	0%
<b>Cardiovascular</b>		
Postural Hypotension	7%	2%
Hypotension	3%	1%
Hypertension	2%	1%
Tachycardia	2%	1%
Hemorrhage	1%	0%
<b>Digestive</b>		
Dry Mouth	19%	3%
Constipation	10%	5%
Dyspepsia	4%	3%
Increased Appetite	2%	1%

Flatulence	2%	0%
Gastrointestinal Disorder	2%	0%
<b>Endocrine</b>		
Hypothyroidism	2%	1%
<b>Hemic and Lymphatic</b>		
Lymphadenopathy	1%	0%
<b>Metabolic and Nutritional</b>		
Weight Gain	6%	3%
Peripheral Edema	4%	2%
<b>Musculoskeletal</b>		
<b>Twitching</b>	4%	0%
<b>Joint Disorder</b>	1%	0%
<b>Nervous</b>		
Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
Hypertonia	4%	3%
Depression	3%	2%
Speech Disorder	3%	1%
Incoordination	2%	1%
Thinking Abnormal	2%	0%
Anxiety	2%	0%
Ataxia	2%	0%
<b>Respiratory</b>		
Pharyngitis	6%	3%
Rhinitis	4%	2%
Sinusitis	2%	1%
<b>Skin and Appendages</b>		
Sweating	2%	1%
<b>Special Senses</b>		
Amblyopia	3%	2%
Ear Disorder	1%	0%

Ear Pain	1%	0%
<b>Urogenital</b>		
Urinary Tract Infection	2%	1%
Female Lactation	1%	0%
Impotence	1%	0%
Urinary Tract Disorder	1%	0%

<sup>1</sup> Reactions for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, nausea, accidental injury, chest pain, face edema, flu syndrome, electrocardiogram abnormal, vomiting, gastritis, SGPT increased, weight loss, nervousness, paresthesia, extrapyramidal syndrome, confusion, cough increased, rash and urinary incontinence.

In bipolar depression studies (up to 8 weeks), the most commonly observed treatment emergent adverse reactions associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (57%), dry mouth (44%), dizziness (18%), and constipation (10%), and lethargy (5%).

Table 9 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 8 weeks) of bipolar depression in 1% or more of patients treated with SEROQUEL (doses of 300 and 600 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

**Table 9. Treatment-Emergent Adverse Reaction Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression<sup>1</sup>**

<b>Body System/ Preferred Term</b>	<b>SEROQUEL (n=698)</b>	<b>PLACEBO (n=347)</b>
<b>Cardiac Disorders</b>		
Palpitations	4%	2%
Tachycardia	1%	0%
<b>Ear and Labyrinth Disorders</b>		
Vision Blurred	4%	2%
<b>Gastrointestinal Disorders</b>		
Dry Mouth	44%	13%
Constipation	10%	4%
Dyspepsia	7%	4%
Vomiting	5%	4%
Gastroesophageal reflux disease	2%	1%
Dysphagia	2%	0%
<b>General Disorders and Administrative Site Conditions</b>		
Fatigue	10%	8%
Asthenia	2%	1%
<b>Injury, poisoning and procedural complications</b>		
Injury	1%	0%
<b>Investigations</b>		
Weight increased	4%	1%
<b>Metabolism and Nutrition Disorders</b>		
Increased Appetite	5%	3%
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Arthralgia	3%	2%
Pain in extremity	2%	1%
<b>Nervous System Disorders</b>		

Somnolence <sup>2</sup>	57%	15%
Dizziness	18%	7%
Lethargy	5%	2%
Akathisia	4%	1%
Extrapyramidal Disorder	3%	1%
Paraesthesia	3%	2%
Dysarthria	3%	0%
Hypersomnia	3%	0%
Tremor	2%	1%
Restless Legs Syndrome	2%	0%
Balance Disorder	2%	1%
Hypoaesthesia	2%	1%
Dystonia	1%	0%
Dizziness, postural	1%	0%
Dyskinesia	1%	0%
Dysgeusia	1%	0%
<b>Psychiatric disorders</b>		
Irritability	3%	1%
Abnormal Dreams	2%	1%
Confusional State	1%	0%
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Nasal Congestion	5%	3%
Cough	3%	1%
Sinus Congestion	2%	1%

## Vascular Disorders

Orthostatic Hypotension	4%	3%
Hypertension	1%	0%

<sup>1</sup>Reactions for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: nausea, upper respiratory tract infection, headache, tinnitus, diarrhea, flatulence, toothache, stomach discomfort, abdominal pain, pyrexia, peripheral edema, nasopharyngitis, influenza, bronchitis, viral gastroenteritis, accidental overdose, decreased appetite, back pain, muscle twitching, myalgia, muscle cramp, headache, insomnia, anxiety, nightmare, libido decreased, suicidal ideation, pollakiuria, dyspnoea, pharyngolaryngeal pain, night sweats and hot flush.

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

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse reaction occurrence on the basis of these demographic factors.

### Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials

*Dose-related Adverse Reactions:* Spontaneously elicited adverse reaction data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse reactions. Logistic regression analyses revealed a positive dose response ( $p < 0.05$ ) for the following adverse reactions: dyspepsia, abdominal pain, and weight gain.

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

The following adverse reactions have also been reported with quetiapine: abnormal dreams and nightmares, hypersensitivity, restless legs syndrome, and elevations in serum creatine phosphokinase (not associated with NMS).

### *Extrapyramidal Symptoms:*

#### *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.

*Adults:* Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates Parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

**Table 10: Adverse experiences potentially associated with EPS in a short-term, placebo controlled multiple fixed-dose Phase III schizophrenia trial (6 weeks duration)**

Preferred term	Placebo (N=51)		SEROQUEL 75 mg/day (N=53)		SEROQUEL 150 mg/day (N=48)		SEROQUEL 300 mg/day (N=52)		SEROQUEL 600 mg/day (N=51)		SEROQUEL 750 mg/day (N=54)	
	n	%	n	%	n	%	n	%	n	%	n	%
Dystonic event <sup>a</sup>	4	7.8	2	3.8	2	4.2	0	0.0	2	3.9	3	5.6
Parkinsonism <sup>b</sup>	4	7.8	2	3.8	0	0.0	1	1.9	1	2.0	1	1.9
Akathisia <sup>c</sup>	4	7.8	1	1.9	1	2.1	0	0.0	0	0.0	1	1.9
Dyskinetic event <sup>d</sup>	0	0.0	2	3.8	0	0.0	0	0.0	1	2.0	0	0.0
Other extrapyramidal event <sup>e</sup>	4	7.8	2	3.8	0	0.0	3	5.8	3	5.9	1	1.9

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

Parkinsonism incidence rates as measured by the Simpson-Angus total score for placebo and the five fixed doses (75,

150, 300, 600, 750 mg/day) were: -0.6; -1.0, -1.2; -1.6; -1.8 and -1.8. The rate of anticholinergic medication use to treat emergent EPS for placebo and the five fixed doses was: 14%; 11%; 10%; 8%; 12% and 11%.

In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

In two placebo-controlled clinical trials for the treatment of bipolar depression using 300 mg and 600 mg of SEROQUEL, the incidence of adverse reactions potentially related to EPS was 12% in both dose groups and 6% in the placebo group. In these studies, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group.

The 3 treatment groups were similar in mean change in SAS total score and BARS Global Assessment score at the end of treatment. The use of concomitant anticholinergic medications was infrequent and similar across the three treatment groups.

### *Children and Adolescents:*

The information below is derived from a clinical trial database for SEROQUEL consisting of over 1000 pediatric patients. This database includes 677 patients exposed to SEROQUEL for the treatment of schizophrenia and 393 patients exposed to SEROQUEL for the treatment of acute bipolar mania.

### **Incidence of Adverse Reactions in Short-Term, Placebo-Controlled Trials in Children and Adolescents**

#### **Adolescents 13 to 17 years of age with Schizophrenia**

The following findings were based on a 6-week placebo-controlled trial in which quetiapine was administered in either doses of 400 or 800 mg/day.

#### *Adverse Reactions Associated with Discontinuation of Treatment*

The incidence of discontinuation due to adverse reactions for quetiapine-treated and placebo-treated patients was 8.2% and 2.7%, respectively. The adverse event leading to discontinuation in 1% or more of patients on SEROQUEL and at a greater incidence than placebo was somnolence (2.7% and 0% for placebo).

*Commonly Observed Adverse Reactions*

In therapy for schizophrenia (up to 6 weeks), the most commonly observed adverse reactions associated with the use of quetiapine in adolescents (incidence of 5% or greater and quetiapine incidence at least twice that for placebo) were somnolence (34%), dizziness (12%), dry mouth (7%), tachycardia ( 7%).

Table 11 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 6-weeks) of schizophrenia in 5% or more of patients treated with SEROQUEL (doses of 400 or 800 mg/day) where the incidence in patients treated with SEROQUEL was at least twice the incidence in placebo-treated patients.

Adverse events that were potentially dose-related with higher frequency in the 800 mg group compared to the 400 mg group included dizziness (8.2% vs. 14.9%), dry mouth (4.1% vs. 9.5%), and tachycardia (5.5% vs. 8.1%).

**Table 11. Treatment-Emergent Adverse Reaction Incidence in a 6-Week Placebo-Controlled Clinical Trial for the Treatment of Schizophrenia in Adolescent Patients**

<b>Body System/Preferred Term</b>	<b>SEROQUEL (n=147)</b>	<b>PLACEBO (n=75)</b>
<b>Central Nervous System Disorders</b>		
Somnolence <sup>1</sup>	34%	11%
<b>Digestive</b>		
Dry Mouth	7%	1%
<b>Cardiovascular</b>		

## Disorders

Tachycardia	7%	0%
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## Nervous System Disorder

Dizziness	12%	5%
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<sup>1</sup>Somnolence combines adverse event terms somnolence and sedation

## Children and Adolescents 10 to 17 years of age with Bipolar Mania

The following findings were based on a 3-week placebo-controlled trial in which quetiapine was administered in either doses of 400 or 600 mg/day.

### *Adverse Reactions Associated with Discontinuation of Treatment*

The incidence of discontinuation due to adverse reactions for quetiapine-treated and placebo-treated patients was 11.4% and 4.4%, respectively. The adverse events leading to discontinuation in 1% or more of patients on SEROQUEL and at a greater incidence than placebo were somnolence (4.1% vs. 1.1%), fatigue (2.1% vs. 0), irritability (1.6% vs. 0) and syncope (1% vs. 0).

### *Commonly Observed Adverse Reactions*

In bipolar mania therapy (up to 3-weeks) the most commonly observed adverse reactions associated with the use of quetiapine in children and adolescents (incidence of 5% or greater and quetiapine incidence at least twice that for placebo) were somnolence (53%), dizziness (18%), fatigue (11%), increased appetite (9%), nausea (8%), vomiting (8%), tachycardia (7%), dry mouth (7%), and weight increased (6%).

Table 12 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 3-weeks) of bipolar mania in 5% or more of patients treated with SEROQUEL (doses of 400 or 600 mg/day) where the incidence in patients treated with SEROQUEL was at least twice the incidence in placebo-treated patients.

Adverse events that were potentially dose-related with higher frequency in the 600 mg group compared to the 400 mg group included somnolence (49% vs. 57%), nausea (6.3% vs. 10.2%) and tachycardia (5.3% vs. 8.2%).

**Table 12 Treatment-Emergent Adverse Reaction Incidence in a 3-Week Placebo-Controlled Clinical Trial for the Treatment of Bipolar Mania in Children and Adolescent Patients**

<b>Body System/Preferred Term</b>	<b>SEROQUEL (n=193)</b>	<b>PLACEBO (n=90)</b>
<b>Nervous System Disorders</b>		
Somnolence <sup>1</sup>	53%	14%
Dizziness	18%	2%
Fatigue	11%	4%
<b>Metabolism and Nutrition Disorders</b>		
Increased Appetite	9%	1%
Weight Increased	6%	0%
<b>Gastrointestinal Disorders</b>		
Nausea	8%	4%
Vomiting	8%	3%
Dry Mouth	7%	0%
<b>Cardiac Disorders</b>		
Tachycardia	7%	0%

<sup>1</sup>Somnolence combines adverse event terms somnolence and sedation

## Adverse Reactions in Schizophrenia and Bipolar Mania Clinical Trials

### *Commonly Observed Adverse Reactions*

In acute therapy for schizophrenia and bipolar mania (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania) the most commonly observed adverse reactions associated with the use of quetiapine in children and adolescents (incidence of 5% or greater and quetiapine incidence at least twice that for placebo) were somnolence (47%), dizziness (15%), fatigue (9%), increased appetite (8%), dry mouth (7%), tachycardia (7%), and weight increased (5%).

Table 13 enumerates the pooled incidence of adverse reactions that occurred during acute therapy of children and adolescents (up to 6 weeks in Schizophrenia and up to 3 weeks in Bipolar Mania). The table includes only those reactions that occurred in 1% or more of patients treated with quetiapine (doses of 400, 600, or 800 mg/day) and for which the incidence in patients treated with quetiapine was greater than the incidence in patients treated with placebo.

**Table 13. Adverse Reactions (incidence  $\geq$  1% and greater than placebo) in Short-Term, Placebo-Controlled Trials of Children and Adolescents (10 to 17 years of age) with Bipolar Mania or Schizophrenia<sup>1</sup>**

<b>Body System/ Preferred Term</b>	<b>SEROQUEL (n=340)</b>	<b>PLACEBO (n=165)</b>
<b>Central/Nervous System Disorder</b>		
Somnolence <sup>2</sup>	47%	15%
Dizziness	15%	4%
Fatigue	9%	4%
Irritability	4%	1%
Tremor	3%	2%
Akathisia	2%	1%
Syncope	2%	0%
Lethargy	1%	0%
<b>Metabolism and Nutrition disorders</b>		

Increased Appetite	8%	2%
Weight Increased	5%	1%
<b>Digestive</b>		
Dry Mouth	7%	1%
<b>Cardiovascular Disorders</b>		
Tachycardia	8%	0%
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Arthralgia	3%	1%
Back Pain	2%	1%
Musculoskeletal Stiffness	2%	1%
<b>Respiratory, thoracic and Mediastinal disorder</b>		
Nasal Congestion	3%	2%
Epistaxis	2%	2%
Upper Respiratory Tract Infection	2%	2%
<b>Gastrointestinal Disorder</b>		
Vomiting	7%	6%
Constipation	2%	2%
Stomach Discomfort	2%	1%
Dyspepsia	2%	2%
<b>Skin and subcutaneous tissue disorders</b>		
Acne	2%	1%
<b>General disorders and administration site conditions</b>		
Pyrexia	2%	1%
Asthenia	2%	1%
<b>Psychiatric Disorders</b>		
Aggression	2%	1%
Restlessness	1%	0%

**Eye Disorders**

Vision Blurred      2%                              1%

**Infections and Infestations**

Tooth Abscess      1%                              0%

<sup>1</sup>Threshold criteria were applied before rounding to the nearest integer

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

***Extrapyramidal Symptoms:***

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 14 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 14 Adverse experiences potentially associated with EPS in the short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration).**

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Preferred term	Placebo (N=75)		Quetiapine 400 mg/day (N=73)		Quetiapine 800 mg/day (N=74)		All Quetiapine	
	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 15 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 15: 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	%	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 dyskinetic 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

### Adverse Reactions in Long-Term Open Label Trial

The adverse reactions reported in a 26-week, open label trial with SEROQUEL in 5% or greater of the children and adolescent patients with schizophrenia or bipolar mania were somnolence (30%), headache (19%), vomiting (11%), increased weight (13%), insomnia (8%), nausea (10%), fatigue (8%), dizziness (9%), increased appetite (7%), upper respiratory tract infection (7%), agitation (5%), tachycardia (5%), and irritability (5%).

### Other Adverse Reactions Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART terms that reflect treatment-emergent adverse reactions as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses  $\geq 75$  mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported reactions are included except those already listed in the tables or elsewhere in labeling, those reactions for which a drug cause was remote, and those reaction terms which were so general as to be uninformative. It is important to emphasize that, although the reactions reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

*Nervous System: Infrequent:* abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased\*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; *Rare:* aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased\*, neuralgia, stuttering, subdural hematoma.

*Body as a Whole: Frequent:* flu syndrome; *Infrequent:* neck pain, pelvic pain\*, suicide attempt, malaise,

photosensitivity reaction, chills, face edema, moniliasis; **Rare:** abdomen enlarged.

**Digestive System:** **Frequent:** anorexia; **Infrequent:** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; **Rare:** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

**Cardiovascular System:** **Infrequent:** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; **Rare:** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

**Respiratory System:** **Frequent:** cough increased, dyspnea; **Infrequent:** pneumonia, epistaxis, asthma; **Rare:** hiccup, hyperventilation.

**Metabolic and Nutritional System:** **Infrequent:** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; **Rare:** glycosuria, gout, hand edema, hypokalemia, water intoxication.

**Skin and Appendages System:** **Infrequent:** pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; **Rare:** exfoliative dermatitis, psoriasis, skin discoloration.

**Urogenital System:** **Infrequent:** dysmenorrhea\*, vaginitis\*, urinary incontinence, metrorrhagia\*, impotence\*, dysuria, vaginal moniliasis\*, abnormal ejaculation\*, cystitis, urinary frequency, amenorrhea\*, female lactation\*, leukorrhea\*, vaginal hemorrhage\*, vulvovaginitis\* orchitis\*; **Rare:** gynecomastia\*, nocturia, polyuria, acute kidney failure.

**Special Senses:** **Infrequent:** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; **Rare:** abnormality of accommodation, deafness, glaucoma.

**Musculoskeletal System:** **Infrequent:** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

**Hemic and Lymphatic System: *Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia.

**Endocrine System: *Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism.

\*adjusted for gender

## 6.2 Vital Signs and Laboratory Values

Hyperglycemia, hyperlipidemia, weight gain, 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)].

### Neutrophil Counts

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 fumarate, 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 at the first sign of a decline in WBC in absence of other causative factors [see *Warnings and Precautions* (5.9)].

### ECG Changes

**Adults:** Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same

criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. In bipolar depression trials, no patients had heart rate increases to > 120 beats per minute. 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. This slight tendency to tachycardia in adults may be related to SEROQUEL's potential for inducing orthostatic changes [*see Warnings and Precautions* (5.8)].

**Children and Adolescents:** In the acute (6 week) schizophrenia trial in adolescents, potentially clinically significant increases in heart rate (> 110 bpm) occurred in 5.2% (3/73) of patients receiving SEROQUEL 400 mg and 8.5% (5/74) of patients receiving SEROQUEL 800 mg compared to 0% (0/75) 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% (1/95) of patients receiving SEROQUEL 400 mg and 2.4% (2/98) of patients receiving SEROQUEL 600 mg compared to 0% (0/98) 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 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 include: 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 in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

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

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

**Divalproex:** Coadministration of quetiapine (150 mg twice daily) 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 is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, erythromycin, and 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:

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was

detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m<sup>2</sup> basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m<sup>2</sup> basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m<sup>2</sup> basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m<sup>2</sup> basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m<sup>2</sup> basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m<sup>2</sup> basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m<sup>2</sup> basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m<sup>2</sup> basis.

There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

## 8.2 Labor and Delivery

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

## 8.3 Nursing Mothers

SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

## 8.4 Pediatric Use

In general, the adverse reactions observed in children and adolescents during the clinical trials 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%).

## Schizophrenia

The efficacy and safety of SEROQUEL in the treatment of schizophrenia in adolescents aged 13 to 17 years were demonstrated in one six week, double-blind, placebo-controlled trial [see *Indications and Usage* (1.1), *Dosage and Administration* (2.1), *Adverse Reactions* (6.1), and *Clinical Studies* (14.1)].

Safety and effectiveness of SEROQUEL in pediatric patients less than 13 years of age with schizophrenia have not been established.

### **Maintenance**

The safety and effectiveness of SEROQUEL in the maintenance treatment of bipolar disorder has not been established in pediatric patients less than 18 years of age. The safety and effectiveness of SEROQUEL in the maintenance treatment of schizophrenia has not been established in any patient population, including pediatric patients.

### **Bipolar Mania**

The efficacy and safety of SEROQUEL in the treatment of mania in children and adolescents ages 10 to 17 years with Bipolar I disorder was demonstrated in a 3-week, double-blind, placebo controlled, multicenter trial. [see *Indications and Usage* (1.2), *Dosage and Administration* (2.2), *Adverse Reactions* (6.1), and *Clinical Studies* (14.2)].

Safety and effectiveness of SEROQUEL in pediatric patients less than 10 years of age with bipolar mania have not been established.

### **Bipolar Depression**

Safety and effectiveness of SEROQUEL in pediatric patients less than 18 years of age with bipolar depression have not been established.

Some differences in the pharmacokinetics of quetiapine were noted between children/adolescents (10 to 17 years of age) and adults. When adjusted for weight, the AUC and C<sub>max</sub> of quetiapine were 41% and 39% lower, respectively, in children and adolescents compared to adults. The pharmacokinetics of the active metabolite, norquetiapine, were similar between children/adolescents and adults after adjusting for weight [see *Clinical Pharmacology* (12.3)].

## **8.5 Geriatric Use**

Of the approximately 3700 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of

SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, 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 SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients [*see Clinical Pharmacology (12) and Dosage and Administration (2)*].

## **9 DRUG ABUSE AND DEPENDENCE**

### **9.1 Controlled Substance**

SEROQUEL is not a controlled substance.

### **9.2 Abuse**

SEROQUEL 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, e.g., 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 reactions or recovered fully from the reported reactions. 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 drugs 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)*]. 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.

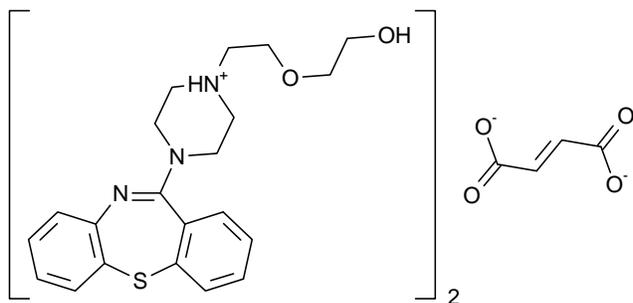
## 10.2 Management of Overdosage

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 overdosage of SEROQUEL. 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. 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<sup>®</sup> (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-piperazinyl)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 is supplied for oral administration as 25 mg (round, peach), 50 mg (round, white), 100 mg (round, yellow), 200 mg (round, white), 300 mg (capsule-shaped, white), and 400 mg (capsule-shaped, yellow) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg and 400 mg tablets contain only yellow ferric oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of SEROQUEL, as with other drugs having efficacy in the treatment of schizophrenia and bipolar disorder, is unknown. However, it has been proposed that the efficacy of SEROQUEL in schizophrenia and its mood stabilizing properties in bipolar depression and mania are mediated through a combination of dopamine type 2 ( $D_2$ ) and serotonin type 2 ( $5HT_2$ ) antagonism. Antagonism at receptors other than dopamine and  $5HT_2$  with similar receptor affinities may explain some of the other effects of SEROQUEL.

SEROQUEL's antagonism of histamine  $H_1$  receptors may explain the somnolence observed with this drug.

SEROQUEL's antagonism of adrenergic  $\alpha_1$  receptors may explain the orthostatic hypotension observed with this drug.

### 12.2 Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain: serotonin  $5HT_{1A}$  and  $5HT_2$  ( $IC_{50s}$ =717 & 148nM, respectively), dopamine  $D_1$  and  $D_2$  ( $IC_{50s}$ =1268 & 329nM, respectively), histamine  $H_1$  ( $IC_{50}$ =30nM), and

adrenergic  $\alpha_1$  and  $\alpha_2$  receptors ( $IC_{50s}=94$  &  $271nM$ , respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors ( $IC_{50s}>5000$  nM).

## 12.3 Pharmacokinetics

### **Adults**

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

### **Children and Adolescents**

At steady-state the pharmacokinetics of the parent compound, in children and adolescents (10-17 years of age), were similar to adults. However, when adjusted for dose and weight, AUC and  $C_{max}$  of the parent compound were 41% and 39% lower, respectively, in children and adolescents than in adults. For the active metabolite, norquetiapine, AUC and  $C_{max}$  were 45% and 31% higher, respectively, in children and adolescents than in adults. When adjusted for dose and weight, the pharmacokinetics of the metabolite, norquetiapine, was similar between children and adolescents and adults [*see Use in Specific Populations* (8.4)].

### **Absorption**

Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with  $C_{max}$  and AUC values increased by 25% and 15%, respectively.

### **Distribution**

Quetiapine is widely distributed throughout the body with an apparent volume of distribution of  $10\pm4$  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.

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 N-desalkyl quetiapine.

### *Age*

Oral clearance of quetiapine was reduced by 40% in elderly patients ( $\geq 65$  years,  $n=9$ ) compared to young patients ( $n=12$ ), and dosing adjustment may be necessary [see *Dosage and Administration* (2)].

### *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 ( $\text{Clcr}=10\text{-}30$  mL/min/ $1.73$  m $^2$ ,  $n=8$ ) had a 25% lower mean oral clearance than normal subjects ( $\text{Clcr} > 80$  mL/min/ $1.73$  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 two of the 8 hepatically impaired patients, AUC and  $C_{\text{max}}$  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)*].

### ***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 Drug Interactions (7.2)*].

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 (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

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

#### Adults

The efficacy of SEROQUEL in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

The results of the trials follow:

1. In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day and 750 mg/day given in divided doses three times per day), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 mg/day to 750 mg/day were generally indistinguishable.
2. In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day given in divided doses three times per day) and low (up to 250 mg/day given in divided doses three times per day) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was superior to placebo on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score.
3. In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day given in divided doses both twice daily and three times daily and 50 mg/day given in divided doses twice daily), only the 450 mg/day (225 mg given twice daily) dose group was superior to the 50 mg/day (25 mg given twice daily) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score..

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 years compared to those older than 40. The clinical significance of this finding is unknown.

## **Adolescents (ages 13-17)**

The efficacy of SEROQUEL in the treatment of schizophrenia in adolescents (13–17 years of age) was demonstrated in a six week, double-blind, placebo-controlled trial. Patients who met DSM-IV diagnostic criteria for schizophrenia were randomized into one of three treatment groups: SEROQUEL 400mg/day (n = 73), SEROQUEL 800 mg/day (n = 74), or placebo (n = 75). Study medication was initiated at 50 mg/day and on day 2 increased to 100 mg/per day (divided and given two or three times per day). Subsequently, the dose was titrated to the target dose of 400 mg/day or 800 mg/day using increments of 100 mg/day, divided and given two or three times daily. The primary efficacy variable was the mean change from baseline in total Positive and Negative Syndrome Scale (PANSS).

SEROQUEL at 400 mg/day and 800 mg/day was superior to placebo in the reduction of PANSS total score.

## **14.2 Bipolar Disorder**

### **Manic Episodes**

#### **Adults**

The efficacy of SEROQUEL in the acute treatment of manic episodes was 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 Young Mania Rating Scale (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 primary rating instrument used for assessing manic symptoms in these trials was YMRS, an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score).

The results of the trials follow:

### *Monotherapy*

The efficacy of SEROQUEL in the acute treatment of bipolar mania was established in 2 placebo-controlled trials. 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 per day.

### *Adjunct Therapy*

In this 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 per day. In a similarly designed trial (n=200), SEROQUEL was associated with an improvement in YMRS scores but did not demonstrate superiority to placebo, possibly due to a higher placebo effect.

### **Children and Adolescents (ages 10-17)**

The efficacy of SEROQUEL in the acute treatment of manic episodes associated with bipolar I disorder in children and adolescents (10 to 17 years of age) was demonstrated in a 3-week, double-blind, placebo controlled, multicenter trial. Patients who met DSM-IV diagnostic criteria for a manic episode were randomized into one of three treatment groups: SEROQUEL 400 mg/day (n = 95), SEROQUEL 600 mg/day (n = 98), or placebo (n = 91). Study medication was initiated at 50 mg/day and on day 2 increased to 100 mg/day (divided doses given two or three times daily). Subsequently, the dose was titrated to a target dose of 400 mg/day or 600 mg/day using increments of 100 mg/day, given in divided doses two or three times daily. The primary efficacy variable was the mean change from baseline in total YMRS score.

SEROQUEL 400 mg/day and 600mg/day were superior to placebo in the reduction of YMRS total score.

### **Depressive Episodes**

## **Adults**

The efficacy of SEROQUEL for the acute treatment of depressive episodes associated with bipolar disorder was established in 2 identically designed 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 Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with scores ranging from 0 to 60. 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. Improvement in symptoms, as measured by change in MADRS score relative to placebo, was seen in both studies at Day 8 (week 1) and onwards. 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

≥ 20 or MADRS score ≥ 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).

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

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on one side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

50 mg Tablets (NDC 0310-0278) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '50' on one side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets, and hospital unit dose packages of 100 tablets.

200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets, and hospital unit dose packages of 100 tablets.

300 mg Tablets (NDC 0310-0274) white, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '300' on the other side, are supplied in bottles of 60 tablets, and hospital unit dose packages of 100 tablets.

400 mg Tablets (NDC 0310-0279) yellow, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '400' on the other side, are supplied in bottles of 100 tablets, and hospital unit dose packages of 100 tablets.

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

## 17 PATIENT COUNSELING INFORMATION

[see Medication Guide]

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL 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. 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.

### 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 [*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)].

#### Need for Comprehensive Treatment Program

SEROQUEL is indicated as an integral part of a total treatment program for adolescents with schizophrenia and pediatric bipolar disorder that may include other measures (psychological, educational, and social). Effectiveness and safety of SEROQUEL have not been established in pediatric patients less than 13 years of age for schizophrenia or less than 10 years of age for bipolar mania. Appropriate educational placement is essential and psychosocial intervention is often helpful. The decision to prescribe atypical antipsychotic medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Medication Guide  
SEROQUEL (SER-oh-kwell)  
(quetiapine fumarate)  
Tablets

Read this Medication Guide before you start taking SEROQUEL 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?**

**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.
- **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?**

- SEROQUEL is a prescription medicine used to treat schizophrenia in people age 13 or older.
- SEROQUEL is a prescription medicine used to treat bipolar disorder, including:
  - depressive episodes associated with bipolar disorder in adults
  - manic episodes associated with bipolar I disorder alone or with lithium or divalproex in adults
  - long-term treatment of bipolar I disorder with lithium or divalproex in adults
- SEROQUEL is used to treat manic episodes associated with bipolar I disorder in children ages 10 to 17 years.

SEROQUEL has not been studied in patients younger than 10 years of age.

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

Before taking SEROQUEL, 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 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 will harm your unborn baby.
- breast-feeding or plans to breast-feed. It is not known if SEROQUEL will pass into your breast milk. You and your healthcare provider should decide if you will take SEROQUEL 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 and other medicines may affect each other causing serious side effects. SEROQUEL may affect the way other medicines work, and other medicines may affect how SEROQUEL 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. Your doctor can tell you if it is safe to take SEROQUEL with your other medicines. Do not start or stop any medicines while taking SEROQUEL 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?**

- Take SEROQUEL exactly as your healthcare provider tells you to take it. Do not change the dose yourself.
- Take SEROQUEL by mouth, with or without food.
- If you feel you need to stop SEROQUEL, talk with your healthcare provider first.

If you suddenly stop taking SEROQUEL, 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, 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?**

Do not drive, operate machinery, or do other dangerous activities until you know how SEROQUEL affects you. SEROQUEL 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. It may make some side effects of SEROQUEL worse.

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

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

**Also, see “What is the most important information I should know about SEROQUEL?” 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 and call your healthcare provider right away.
- **High blood sugar (hyperglycemia):** Increases in blood sugar can happen in some people who take SEROQUEL. 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 and during therapy.

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

- 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. 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 and during therapy.

- **Increase in weight (weight gain):** Weight gain has been seen in patients who take SEROQUEL 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. Tardive dyskinesia may also start after you stop taking SEROQUEL.
- **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 and during therapy.
- **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 tests to check your prolactin levels.
- **Increases in liver enzymes:** Your healthcare provider may do blood tests to check your liver enzyme levels.
- **Long lasting and painful erection**
- **Difficulty swallowing**

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

Adults

- |                  |   |
|------------------|---|
| • drowsiness     | • upset stomach                                 |
| • dry mouth      | • weight gain                                   |
| • dizziness      | • a sudden drop in blood pressure upon standing |
| • weakness       | • abnormal liver tests                          |
| • abdominal pain |   |
| • constipation   |   |
| • sore throat    |   |
| • sluggishness   |   |

Children and Adolescents:

- drowsiness
- fatigue
- nausea
- dry mouth
- weight gain
- dizziness
- increased appetite
- vomiting
- rapid heart beat

These are not all the possible side effects of SEROQUEL. 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?**

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

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

Do not take SEROQUEL unless your healthcare provider has prescribed it for you for your condition. Do not share SEROQUEL 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. For more information about SEROQUEL, talk with your healthcare provider or pharmacist or call 1-800-236-9933. You can ask your healthcare provider for information about SEROQUEL that is written for health professionals.

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

**Active ingredient:** quetiapine fumarate

**Inactive ingredients:** povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol, and titanium dioxide. The 25 mg tablets contain red and yellow ferric oxide. The 100 mg and 400 mg tablets contain only yellow ferric oxide

#### **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:**

- 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.

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

SEROQUEL is a trademark of the AstraZeneca group of companies.

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Wilmington, DE 19850

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SIC XXXX-XX

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**020639Orig1s046**

**REMS**

**NDA 20-639**  
**SEROQUEL<sup>®</sup> (quetiapine fumarate) 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<sup>®</sup> (quetiapine fumarate) Tablets.

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

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

A currently approved Medication Guide will be dispensed with each SEROQUEL 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.

In accordance with 21 CFR 208.24(d) a statement will be included on the container label for SEROQUEL 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:*

**020639Orig1s046**

**SUMMARY REVIEW**

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

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**DATE:** 2 December 2009

**FROM:** Mitchell V. Mathis, M.D.  
Deputy Director  
Division of Psychiatry Products, HFD-130

**TO:** File NDA 20-639 S-045, S-046

**SUBJECT:** Approval Recommendation for Seroquel [quetiapine fumarate)] Tablets for the Treatment of Schizophrenia (ages 13-17) and the Acute Treatment of Manic Episodes Associated with Bipolar Disorder (ages 10-17) in Children and Adolescents

**BACKGROUND AND REGULATORY HISTORY**

Seroquel is an atypical antipsychotic approved in adults for the treatment of schizophrenia, the acute treatment of depressive episodes associated with bipolar disorder, and the acute treatment of manic episodes associated with bipolar I disorder. The sponsor submitted one positive short-term trial in adolescents with schizophrenia (ages 13-17) and in one trial of children and adolescents with manic episodes associated with bipolar I disorder (ages 10-17), as well as pharmacokinetic data to support dosing in this population, and longer-term (6 months) safety data.

The Division was prepared to approve these applications after reviewing the data (see team member reviews, this NDA), but decided to first take this application (along with two others pending for similar indications) to the Psychopharmacologic Drugs Advisory Committee (PDAC) for a public discussion among experts in the fields of child psychiatry, general psychiatry, drug safety, cardiology, and endocrinology. We were specifically interested in expert opinion about expanding the indications of atypical antipsychotics into broader populations, especially given the adverse metabolic profile and yet unquantified risk of tardive dyskinesia with this class of medications.

Seroquel (and others in the atypical antipsychotic class) has an adverse impact on glucose, lipids, and weight gain. Since schizophrenia and bipolar I disorder are life-long illnesses, our concern was that pediatric patients with these disorders would be treated earlier in life and for an extended period of time compared to adults, therefore increasing exposure-related risks of adverse reactions associated with drugs in this class.

Our safety review revealed that younger patients experienced qualitatively similar adverse reactions as adults, but there were some quantitative differences related to adverse changes in metabolic parameters, as well as other adverse events. Our belief has been that pediatric patients represent a more treatment-naïve population, and so effects on glucose, lipids and weight are more apparent in this population, but we wanted to hear from experts and discuss these issues in public before taking a final action.

## **PEDIATRIC ADVISORY COMMITTEE MEETING (PDAC)**

The PDAC met on June 9-10, 2009. The members agreed with us that efficacy had been established in the studied populations for both indications. We then discussed the safety issues of concern with the committee at length. From a discussion of the facts and from the experience of treating physicians, it was obvious that schizophrenia and bipolar I disorder affect the pediatric population (in fact these diseases often onset during the pediatric years) and that the availability of multiple treatment options is important to the clinical management of these routinely devastating disorders. It was noted that the American Academy of Child and Adolescent Psychiatry (AACAP) recommends in its practice guidelines that antipsychotics be used in both disorders, and it was routinely accepted that children and adolescents were already being treated with atypical antipsychotics, including Seroquel, because their safety profiles are considered by many clinicians to be superior to the typical antipsychotics which have a known exposure-related risk of tardive dyskinesia.

The votes of the PDAC were as follows:

- Schizophrenia
  - Effective? 17 yes; 1 no
  - Safe? 16 yes; 0 no; 2 abstain
- Bipolar Mania
  - Effective? 17 yes; 0 no; 1 abstain
  - Safe? 13 yes; 0 no; 5 abstain

## **LABELING/MEDICATION GUIDE**

The labeling and Medication Guide were updated to include the pediatric indications, and pediatric safety data (which had largely already been included in labeling). We also included a new section in labeling entitled *Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder*, which states that diagnosing these illnesses in children/adolescents is difficult, and that medication management is but one part of a comprehensive treatment program necessary to provide optimal care. *Dosing and Administration* describes what we learned from the trials about dosing younger patients, and is presented in an easy to read tabular form in Highlights. The Medication Guide was updated to include a comprehensive description of what can be expected when using the drug, and when the patient/parent should call the prescriber. The Office of Safety and Epidemiology were consulted to evaluate the Medication Guide and the safety review team reviewed the final REMS documents.

## **CONCLUSIONS**

The safety and efficacy of Seroquel has been established in pediatric patients with schizophrenia and manic episodes associated with bipolar I disorder. My recommendation to the Director is to approve these indications, with the expanded labeling and Medication Guide. This action will provide clinicians treating these patients with the proper information about dosing, a complete description of the risks of treating pediatric patients with Seroquel, and a comprehensive Medication Guide to provide to patients with their prescription. This will be a substantial improvement for clinicians treating pediatric patients suffering from these debilitating diseases.

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

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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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MITCHELL V Mathis  
12/02/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**020639Orig1s046**

**MEDICAL REVIEW(S)**

**Review and Evaluation of Clinical Data  
NDAs 20-639 (S-55) and 22-047 (S-28)**

**Sponsor:** AstraZeneca, Pharmaceuticals LP.  
**Drug:** NDA 20-639/Seroquel (quetiapine fumarate) Tabs  
NDA 22-047/Seroquel XR (quetiapine fumarate) Tabs  
**Therapeutic Class:** Atypical antipsychotic  
**Dosage and Route:** 25 mg, 50 mg, 100 mg, 200 mg, 300 mg and 400 mg tablets  
**Indications:** Schizophrenia, Schizophrenia maintenance, Bipolar depression, Bipolar mania, Bipolar maintenance and Major depressive disorder adjunctive therapy with antidepressants  
**Material Submitted:** Prior Approval Supplement - Proposed REMS Modification: Elimination of REMS  
**Correspondence Date:** NDA 20-639 (07/19/2011) and NDA 22-047 (07/20/2011)  
**Submission Numbers:** NDA 20-639/SDN# 402 and NDA 22-047/SDN# 157  
**Review Completion Date:** 09/13/2011

**I Background**

The Risk Evaluation and Mitigation Strategy (REMS) for Seroquel and Seroquel XR was initially approved on December 2, 2009 as part of the Approval Letter for pediatric efficacy supplements regarding the use of Seroquel in the treatment of Schizophrenia (ages 13-17 yrs) (NDA20639/S-45), and the acute treatment of manic episodes associated with Bipolar Disorder (ages 10-17 yrs) (NDA20639/S-46). The REMS consists of Medication Guide (MedGuide) only.

Per the December 2, 2009 letter, the goal of Seroquel MedGuide only REMS was to inform patients about serious risks associated with use of Seroquel, the specific new risks communicated in this MedGuide only REMS included hyperglycemia, hyperlipidemia, and weight gain. Another REMS element included in that letter was future timetable for submission of assessments listed as 18-month, 3 and 7 years after initial approval. Seroquel REMS also required the sponsor to assess the effectiveness of the REMS in reaching its goal.

Since the initial approval of MedGuide only REMS, the sponsor has submitted modifications for the MedGuide twice, in their submission dated May 26, 2010 (resubmitted as Prior Approval labeling supplement on December 16, 2010) under NDA 20-639/SLR-051 and NDA 22-047/SLR-024, and another MG change submission dated March 25, 2011 under NDA 20-639/SLR-049 and NDA 22-047/SLR-23. Proposed modification included minor MedGuide changes. In the SLR-051 and 024 submissions, the sponsor's proposal included a statement in the MedGuide that patients should inform their healthcare provider if they are having a urine drug screen (UDS) as Seroquel may affect the test results. This set of supplements was reviewed by Kofi Kumi, Ph.D., Office of Clinical Pharmacology (review dated 11/29/10); he recommended approval of the proposed changes. Additionally, Mary Dempsey, OSE/Division of Risk Management (DRISK) also reviewed these changes. In her review dated March 1, 2011, she noted that on February 25, 2011, FDA published a draft Guidance "Guidance for Industry: Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)" that states based on the risks of a drug and public health concern, FDA has the authority to determine whether a MedGuide should be required as part of a REMS or should be required as labeling but not part of a REMS. Based on the newly published draft guidance, DRISK determined that REMS for Seroquel is not necessary and that the sponsor can be released from their REMS requirements.

On May 31, 2011 the sponsor submitted the REMS 18-month assessment for Seroquel and Seroquel XR (S-45 and S-46). The sponsor had conducted a patient questionnaire survey to assess the effectiveness of REMS in meeting its goal of informing patients about the serious risks associated with the use of Seroquel. The survey had assessed the following:

- Patient's awareness of the serious risks of increased mortality in elderly patients with dementia and an increased risk of suicidal thinking and behavior in children, adolescents and young adults.
- Patient's awareness of the serious risks of developing hyperglycemia, hyperlipidemia and weight gain.
- Distribution of the Medication Guide to patients.

In this submission, on July 19, 2011, the sponsor submitted a letter proposing a REMS modification to eliminate the REMS for Seroquel (NDAs 20-639, S-55) and Seroquel XR (NDA 22-047, S-28). The sponsor believes that maintaining the MedGuide for Seroquel and Seroquel XR as part of the approved labeling, and not part of REMS, is sufficient and appropriate.

On July 21, 2011, we met with OSE/ DRISK, and Division of Pharmacovigilance for a 50-Day meeting to discuss the OSE findings based on the data in the REMS 18-month assessment report.

Jeanne Perla, Ph.D., from DRISK completed her 18-month REMS assessment review (dated 08/08/2011) for Seroquel and Seroquel XR. A total of 452 eligible patients or caregivers completed the patient questionnaire survey. About 60-98% respondents had a variable awareness of the risk of suicidality and the signs and symptoms of when to notify their health care provider. Around 47% respondents had a marginal understanding of the risk of hyperglycemia and around 70% had a marginal awareness of the propensity towards weight gain. Approximately 31% respondent's demonstrated poor awareness of the risks of mortality in the elderly demented population and the same percentage showed lack of understanding for hypercholesterolemia. In summary, she notes that the MedGuide is being provided to the patients, risk messages of suicidal thoughts, hyperglycemia and weight gain were most understood, and least understood were risk messages of death in elderly with dementia and hyperlipidemia. Though the sponsor proposed no specific modifications to the Seroquel and Seroquel XR MedGuide, they did propose the following:

- Sponsor will test the readability and comprehension of mortality in elderly patients with dementia, and hyperlipidemia sections of the MedGuide.
- The sponsor will notify pharmacies of the requirement to dispense the Seroquel MedGuide with each prescription and how patients can obtain additional copies of the MedGuide.

Dr. Perla's review concluded that a 90-day discussion period needs to be initiated with the intention of revising the Seroquel MedGuide, as the REMS goal was being partially met and for Seroquel MedGuide to become consistent with the recently approved MedGuide modifications (06/21/2011) of Symbyax (NDA-021520, S-31 and S-32) and Zyprexa (NDA-020592, S-60 and S-61).

The sponsor was informed of FDA initiating a 90-day discussion period through an email communication sent by Kimberly Updegraff, RPh, MS, RAC on July 26, 2011.

Additionally, Kimberly Updegraff through another email communication had requested the sponsor to provide an update status of any studies/trials involving Seroquel/Seroquel XR. On July 26, 2011, the sponsor responded through an email stating "there are no ongoing IND studies for Seroquel or Seroquel XR at this time."

The Patient Labeling Team, (OSE/OMEPRM) reviewed the 18-month REMS assessment report as well. Twanda Scales, BSN, RN (Patient labeling reviewer from DRISK) in her review (dated 08/10/2011) has recommended changes to the Seroquel MedGuide. The changes are based on REMS 18-month review

report stating REMS was not meeting its goal, thus these changes include placing the most important information on the first page and having the Seroquel Medguide be comparative to an already approved MedGuide for Symbyax and Zyprexa. The changes focused on “What is the most important information I should know about TRADENAME?” section. The goal being that Seroquel, Seroquel XR, Symbyax and Zyprexa MedGuide should have comparable information provided in their MedGuide.

## **II Conclusions and Recommendations**

The REMS 18-month review is complete, REMS assessment team stated they did not feel that Seroquel REMS was meeting its goal. They stated that the respondents of the survey had variable awareness of the risks of suicidality, and the signs and symptoms of when to notify their healthcare provider. Additionally, respondents demonstrated poor awareness of mortality in the elderly demented population and hyperlipidemia, and demonstrated a marginal awareness of hyperglycemia and the propensity for weight gain. Thus, the assessment team agreed that the MedGuide needed to be revised and thus the 90-day discussion period was opened on July 26, 2011. As a result of the 18 month REMS assessment, the Patient Labeling Team recommended changes to the MedGuide that are noted in their annotated MedGuide review. The MedGuide changes are consistent with the recently approved MedGuide format and content of Symbyax and Zyprexa.

I concur that the REMS requirement can be removed for REMS for Seroquel and Seroquel XR. The supplement approval letter should include the action to eliminate the REMS, only after the MedGuide revisions for consistency with the comparators like Symbyax and Zyprexa are complete and accepted by the sponsor, and at that time we can close the 90-day discussion period. The MedGuide from hereon will be a part of the approved labeling in accordance with 21 CFR 208, and MedGuide changes will be approved under safety label changes.

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Kavneet Kohli-Chhabra M.D  
Medical Reviewer  
FDA/CDER/OND/DPP/HFD 130

cc: NDA 20639 and 22-047/HFD 130  
KUpdegraff  
KKohli-Chhabra  
NKhin  
TLaughren  
MMathis  
VCrentsil

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KAVNEET-RIPI KOHLI-CHHABRA  
09/13/2011

NI A KHIN  
09/13/2011

**MEMORANDUM**

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

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**DATE:** August 13, 2009

**FROM:** Ni A. Khin, M.D.  
Team Leader  
Division of Psychiatry Products, HFD-130

**TO:** File NDA 20-639/SE1-045 and 046  
(This overview should be filed with the 10-28-2008 original submission)

**SUBJECT:** Recommendation of Approval Action for quetiapine fumarate (Seroquel®) in the treatment of Schizophrenia in Adolescents (13 to 17 yrs) and Pediatric Bipolar Mania (10 to 17 yrs)

**1. BACKGROUND**

Quetiapine fumarate (Seroquel®) is an atypical antipsychotic agent. In the U.S., the immediate release (IR) oral formulation of quetiapine (NDA 20-639) was first approved in September 1997 for the treatment of schizophrenia. It is also approved for the treatment of Bipolar I disorder, acute mania and depression. Quetiapine's efficacy in schizophrenia and bipolar disorder is thought to be mediated through a combination of dopamine D2 and serotonin 5-HT<sub>2</sub> antagonism. The extended release tablets (Seroquel XR) was approved on May 17, 2007 (NDA 22-047). In adults, the approved dose range of Seroquel in the treatment of schizophrenia is 400-800 mg/day. In bipolar disorder, the approved dose range is 300 to 600 mg/day for bipolar depression and 400 to 800 mg/day for bipolar mania in adults. The Seroquel oral tablet formulation is available as 25, 50, 100, 200, 300, and 400 mg strength.

On February 11, 2003, the Agency has issued a pediatric written request letter to the sponsor. In response to the WR, the sponsor submitted protocols for pivotal efficacy and safety studies (protocols 112, 149 and 150) under IND 32,132 in May 2004.

On October 28, 2008, the sponsor has submitted supplemental new drug applications for marketing approval of Seroquel in treatment of schizophrenia in adolescents (age 13 to 17 yrs) and Bipolar I Disorder, acute mania in children and adolescents (age 10 to 17 yrs). In this set of NDA supplements, the sponsor included the results from two pivotal protocols: study D1441C00112 (Study 112) in adolescent patients with schizophrenia and D1441C00149 (Study 149) in children and adolescents with bipolar mania. In addition, the application included data from a pediatric PK study D1441C00028 (Study 028) and an open label safety study D1441C00150 (Study 150). The

(b) (4)

This NDA has been reviewed by Julia Pinto, Ph.D, CMC reviewer from ONDQA (review dated 4/16/09), Phillip Dinh, Ph.D., Statistical Reviewer, the Office of Biostatistics (review dated

4/13/09), Kofi Kumi, Ph.D., Clinical Pharmacologist, Office of Clinical Pharmacology (review dated 3/12/09), and Cara Alfaro, Pharm.D., Clinical Analyst, DPP (review dated 5/11/2009 and addendum dated 08/11/2009).

## **2.0 CHEMISTRY**

There was no new CMC information required for review in this submission as all CMC information is cross-referenced to the original NDA. In the Chemistry review, Dr. Pinto noted that an environmental assessment conducted by Raanan Bloom, Ph.D., from the Office of New Drug Quality Assessment in December 2007 is valid through 2011. The EA was found acceptable and recommended as FONSI (no significant impact). From the CMC perspective, this set of supplements is recommended for approval.

## **3.0 PHARMACOLOGY/TOXICOLOGY**

There is no new pharmacology/toxicology data presented in this submission.

## **4.0 CLINICAL PHARMACOLOGY**

OCP reviewed data from the pediatric PK study (Study 28). There was a tendency for children (10 - 12 years of age) to have higher exposure of quetiapine (AUC 36% – 55% and Cmax 54% - 71% higher) than the levels observed in adolescents (13 to 17 years). Dose normalized exposures were generally lower (AUC = 12% lower and Cmax = 8% lower) in pediatric patients than adults. Dose normalized, weight-normalized AUC and Cmax decreased by about 40% in pediatric population (10 to 17 yrs) when compared to adults. These differences are not expected to be clinically relevant.

In addition, the OCP-Pharmacometric Team, Hao Zhu, Ph.D., and Christine Garnette, Pharm.D., provided their assessment of QT data from the two pediatric pivotal studies. Based on the evaluation by the quetiapine concentration-QTcF relationship modeling derived from data from a thorough QT study in healthy adults, quetiapine does not appear to prolong QTc interval in children and adolescents at the proposed clinical doses. Specifically, the largest observed mean QTcF interval change from baseline observed in the clinical trial was around 2 ms (i.e., approximately 4 ms difference in study 112 and no difference between the quetiapine and placebo in study 149). No patients had QTcF values above 500 ms or mean change from baseline in QTcF greater than 60 ms in both pediatric studies.

They also provided some labeling comments for the pediatric clinical pharmacology section.

## **5.0 CLINICAL DATA**

### **5.1 Efficacy Data**

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

##### **Schizophrenia in Adolescents**

Our review of efficacy was mainly based on the result of Study D1444CC00112 (Study 112) which was a fixed dose, multicenter, double-blind, randomized, placebo controlled study to evaluate the

efficacy and safety of quetiapine fumarate (QTP IR doses of 400 mg/day and 800 mg/day administered bid or tid) in adolescent patients (13 to 17 yrs of age) with schizophrenia after 6 weeks of treatment.

The sponsor indicated that results of this study 112 demonstrated that QTP (both 400 and 800 mg/day doses) was superior to placebo on the primary efficacy variable (i.e., change from baseline to final visit in PANSS total score).

### **Pediatric Bipolar I Disorder, Acute Mania (Monotherapy)**

Our review of efficacy was mainly based on the result of Study D1444CC00149 (Study 149) which was an international, multicenter, double-blind, randomized, placebo controlled, fixed dose (QTP IR 400 mg/day and 600 mg/day administered bid or tid) study to evaluate the efficacy and safety of QTP as monotherapy in children and adolescent patients (10 to 17 yrs of age) with bipolar I disorder, acute mania, after 3 weeks of treatment.

The sponsor indicated that results of this study 149 demonstrated that QTP (both 400 and 600 mg/day doses) was superior to placebo on the primary efficacy variable (i.e., change from baseline to final visit in YMRS total score).

I would briefly describe the results of each of these studies in the following subsection.

#### **5.1.2 Summary of Studies Pertinent to Efficacy Claim**

##### **5.1.2.1 Adolescent Schizophrenia - Study D1444CC00112 (Study 112)**

This was a 6-week, international, multicenter, randomized, double-blind, parallelgroup, placebo-controlled study of the efficacy and safety of quetiapine fumarate (Seroquel) immediate-release tablets in daily doses of 400 mg and 800 mg compared with placebo in the treatment of adolescents (aged 13 to 17 yrs) with schizophrenia who met a DSM-IV diagnosis of schizophrenia and confirmed by the K-SADS-PL. After screening, eligible patients who entered into a 6 week double-blind treatment were randomized to receive QTP IR 400 mg/day, 800 mg/day or placebo, oral dose given bid or tid. The QTP IR dose was titrated to 300 mg/day within 4 days: 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3, 300 mg on Day 4 and a fixed target dose was reached on Day 4 for the QTP 400 mg/day group, and on Day 9 for the QTP 800 mg/day group.

The study was started in October 2004 and completed in June 2007. It was conducted at 46 centers around the world (total N=268) including the U.S. (23 sites; n=88), Russia (4 sites; n=40), Serbia (4 sites; n=31), Ukraine (3 sites; n=28), Poland (2 sites; n=9), Germany (n=1), the Philippines (4 sites; n=46), India (2 sites; n=11), Malaysia (2 sites; n=8) and South Africa (n=6).

Out of a total of 268 patients enrolled in the study, 46 were screen failures and 222 subjects randomized to the double-blind treatment. The MITT samples for quetiapine IR 400 mg, 800 mg and placebo were 73, 74, and 75, respectively. A total of 164 subjects (74%) completed the double-blind study; QTP groups had higher completion rates: 56 (76.7%) in QTP IR 400 mg/day group, 61 (82.4%) in QTP IR 800 mg/day group and 47 (62.7%) in the placebo group. 58 subjects discontinued from the study; 17, 13 and 28 in the QTP IR 400 mg, 800 mg and the placebo

respectively. The most common reason for discontinuation from the study was adverse events in QTP IR group; and lack of efficacy and voluntary discontinuation by patient in the placebo group.

The subjects enrolled were mostly Caucasian (61%), mean age was 15.4 yrs, and had approximately 58% male subjects. Approximately 70% were diagnosed with schizophrenia, paranoid type. Mean baseline PANSS total score was 96; mean baseline body weight was 61 kg. There seemed to be no significant differences in baseline demographic and disease characteristics among the treatment groups.

The efficacy assessment included the Positive and Negative Symptoms Scale (PANSS), and the CGI rating scales. The ITT was defined as all randomized patients who were given study treatment and who had baseline and at least one post-baseline PANSS assessment. The primary outcome variable was the change from baseline in the PANSS total score at final visit (Day 42). The primary analysis was MMRM (unstructured covariance pattern). Baseline PANSS total score was used as a covariate, other variables in the model included treatment, region, visit, and visit-by-treatment interaction. The LOCF method using ANCOVA model was also done as sensitivity analysis. Dr. Dinh confirmed the sponsor’s efficacy results. The primary efficacy results can be seen in Table 1 below:

Table 1: Primary Efficacy Results on Change from baseline to endpoint in total PANSS Scores (MMRM)

Treatment Groups	N	Baseline PANSS Total		Endpoint PANSS Total		LSMean Change	LSMean Difference	p-value (vs. placebo)
		Mean	SD	Mean	SD			
Quetiapine 400 mg	54	96.9	16.41	72.5	20.35	-27.31	-8.16	0.043
Quetiapine 800 mg	55	98.4	15.73	70.3	17.28	-28.44	-9.29	0.009
Placebo	43	97.5	16.4	78	23.32	-19.15		

Comment: Both Drs. Alfaro and Dinh considered this a positive study for Seroquel IR, and I agree with them.

**5.1.2.2 Bipolar Disorder, Acute Mania (Monotherapy) - Study D1444CC00149 (Study 149)**

This was a 3 week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, fixed dose (daily dose 400 and 600 mg) study comparing the effect of QTP IR and placebo in children and adolescents (aged 10 to 17 yrs) patients who met a DSM-IV diagnosis of bipolar I mania, confirmed by the K-SADS-PL. After screening/washout period, eligible patients who entered into a 3 week treatment period were randomized to receive QTP IR 400 mg/day, 600 mg/day or placebo, oral dose given bid or tid by the judgment of the investigator. Randomization was stratified by age (10-12 yrs, 13-17 yrs). QTP IR was titrated to the target fixed doses of 400 mg/day by Day 5 and 600 mg/day by Day 7.

The study was started in August 2004 and completed in July 2006. It was conducted at 34 centers in the U.S. Out of a total of 393 patients enrolled in the study, 284 subjects randomized to the double-blind treatment. The ITT samples for quetiapine IR 400 mg, 800 mg and placebo were 95, 98, and 90, respectively. A total of 222 subjects (74%) completed the double-blind study; QTP groups had higher completion rates: 76 (80%) in QTP IR 400 mg/day group, 80 (81.6%) in QTP IR

600 mg/day group and 66 (72.5%) in the placebo group. 62 subjects discontinued from the study; 19, 18 and 25 in the QTP IR 400 mg, 600 mg and the placebo respectively. The most common reason for discontinuation from the study was adverse events in QTP IR group; and lack of efficacy and voluntary discontinuation by patient in the placebo group.

The subjects enrolled were mostly Caucasian (76%), mean age was 13 yrs, and had approximately 55% male subjects. Mean baseline YMRS total score was 30. There seemed to be no significant differences in baseline demographic and disease characteristics among the treatment groups. Approximately 43% of enrolled subjects also had comorbid ADHD with a slightly higher percentage (52%) of subjects enrolled in QTP 400 mg/day group.

The efficacy assessment included the Young Mania Rating Scale (YMRS), and the CGI rating scales. The primary outcome variable was the change from baseline in the YMRS total score at final visit (Day 21). The MITT analysis set included all randomized patients who received at least 1 dose of study treatment and who had a randomization (baseline) value and at least one post-randomized YMRS assessment, classified by the randomized treatment assignment. The primary analysis was MMRM (unstructured covariance pattern). Baseline YMRS total score was used as a covariate, other variables in the model included treatment, region, visit, and visit-by-treatment interaction. The LOCF method using ANCOVA model was also done as sensitivity analysis. Dr. Dinh confirmed the efficacy results. The primary efficacy results can be seen in Table 2 below:

Table 2: Efficacy Results on Change from baseline in total YMRS Scores at endpoint (MMRM)

Treatment Groups	N	Baseline YMRS Total		Mean change from baseline to endpoint		LSMean Change	LS Mean Difference	P-value vs. placebo
		Mean	SD	Mean	SD			
Quetiapine 400 mg	76	29.2	5.9	-15.3	8.45	-14.25	-5.21	<0.001
Quetiapine 600 mg	81	29.2	5.96	-15.8	9.32	-15.06	-6.56	<0.001
Placebo	67	30	5.45	-10.1	10.28	-9.04		

Comment: Both Drs. Alfaro and Dinh considered this a positive study for quetiapine, and I agree with them.

### 5.1.3 Comments on Other Important Clinical Issues

#### 5.1.3.1 Predictors of Treatment Response

Exploratory subgroup analyses based on age (<15 yrs; >15 yrs), gender (Males, Females), race (Caucasian, others), and geographic regions (US vs. non-US) was conducted for schizophrenia study 112. As noted in detail by Dr. Dinh in the FDA statistical review, the results trended in the same direction in favor of seroquel in both the race or gender subgroups. Quetiapine appeared to show a significantly greater treatment effect in the <15 yrs age group. For the >15 yrs group, there seemed a larger placebo effect. Quetiapine appeared to show a greater improvement of treatment effect among the US patients than non-US patients.

Exploratory subgroup analyses based on age (<10-12 yrs; >13-17 yrs), gender (Males, Females), and race (Caucasian, others) was also conducted for bipolar mania study 149. The results trended in the same direction in favor of QTP in all these subgroup analyses.

#### 5.1.3.2 Duration of Treatment

In adults, quetiapine IR is currently approved for the maintenance treatment of Schizophrenia and Bipolar I disorder, mania, as adjunct therapy to lithium or divalproex; no maintenance indication has been granted for quetiapine IR for monotherapy. No well-controlled longer term efficacy studies were conducted in pediatric population.

#### 5.1.3.3 Effect Size

Treatment effect (observed as change from baseline to endpoint in PANSS total about 7-8 points for schizophrenia and YMRS total scores around 5 points for bipolar mania) seemed reassuringly similar to those observed in other drug trials.

#### 5.1.3.4 Dose Response

The treatment response seems numerically greater in the higher dose QTP IR groups for both pediatric indications (i.e., the placebo-subtracted LS mean PANSS total difference of -8.16 in the 400 mg vs. -9.29 in the 800 mg quetiapine groups in the schizophrenia study 112; the placebo-subtracted LS mean difference in YMRS total of -5.2 in the 400 mg vs. -6.6 in the 600 mg quetiapine group for the bipolar mania study 149).

#### 5.1.3.5 Secondary Measures

No key secondary endpoint was pre-specified in either study.

### 5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analysis of study 112 supported the efficacy claim of Seroquel IR for acute treatment of schizophrenia in adolescents. The efficacy analysis of study 149 also supported the efficacy claim of Seroquel IR for acute monotherapy treatment of bipolar I mania in the pediatric population.

(b) (4)

## 5.2 Safety Data

### 5.2.1 Safety Database

Dr. Alfaro's safety review of this set of NDA supplements was based on the safety data from above two studies: study 112 and 149, in addition to safety data from the 26 week open label flexible dose study (study 150). In study 112, the safety population consisted of 222 subjects in which 73 and 74

subjects were exposed to fixed doses of QTP IR 400 mg and 800 mg respectively for a mean duration of 40 days. The safety population of 283 subjects for Study 149 included 95 patients in the quetiapine 400 mg/day group, 98 patients in the quetiapine 600 mg/day group and 75 patients in the placebo group for a mean duration of 20.5 days.

The safety population for Study 150 included 381 patients treated with open-label quetiapine for mean duration of 146 days [mean daily dose 599 (256.8) mg over a median of 181 days on study medication]; 237 (62.2%) completed the study. In pooled analysis for studies 112 and 149, most patients remained on the bid dosing schedule and 18.8% were switched to a tid dosing based on tolerability issues as per the clinical judgment of the investigator.

No deaths reported in all trials included in this submission. Similar percentage of serious adverse events occurred in the QTP group as compared to the placebo group. The majority of events were potentially related to underlying psychiatric diagnosis. For the AE dropouts, the most common adverse events associated with subject discontinuation were somnolence, sedation, lethargy and fatigue.

## 5.2.2 Safety Findings and Issues of Particular Interest

### 5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is approximately twice or more the placebo risk). The sponsor reported the following most common adverse events in the quetiapine IR group for study 112 and 149: somnolence/sedation, dizziness, fatigue, dry mouth, tachycardia, increased weight and increased appetite. As noted by Dr. Alfaro in her review, the dose related signal for frequencies of common AEs appears likely for sedation/somnolence, dizziness, dry mouth and tachycardia.

### 5.2.2.2 Metabolic Effects

#### Glucose, Lipid Profile and Prolactin

As can be seen in Table below, QTP IR was associated with mean change from baseline to endpoint increases in total cholesterol, LDL triglycerides, and prolactin. Mean change in glucose was a decrease in Study 112 and an increase in Study 149. Similarly, prolactin concentrations decreased in Study 112 and increased in Study 149. Overall, male patients had a greater elevation in prolactin compared to females.

Table 3: Mean Changes from Baseline to Endpoint for Select Laboratory Tests

	Study 112			Study 149		
	QTP 400 mg (n=73)	QTP 800 mg (n=74)	Placebo (n=75)	QTP 400 mg (n=95)	QTP 600 mg (n=98)	Placebo (n=90)
Fasting glucose (mg/dL)	-0.07	-1.4	-1.7	3.5	3.8	-1.17
HbA1c (%)	0.02	0.06	-0.005	-0.001	0.05	0.16
Total Cholesterol (mg/dL)	7.8	7.4	-8	7.8	7.6	-3.3
LDL (mg/dL)	8.6	4.8	-3.9	5.6	2.9	-0.48
Triglycerides (mg/dL)	9.6	15.6	-8.2	11.17	30.6	-8.7
Prolactin (ng/ml)	-10.5	-7.8	-18.2	2.8	1.86	-1.15

The sponsor also conducted outlier analysis. There were a higher percentage of patients who were noted to have shifts from normal to important high in these parameters in the QTP IR treated patients as compared to placebo. The cut-off values included glucose  $\geq 126$ ,  $>200$  mg/dL; total cholesterol  $>240$  mg/dL; triglyceride  $\geq 200$  mg/dL; prolactin  $>20$  (M) or 26 ng/ml (F)].

	Study 112: Shift to High, n(%)			Study 149: Shift to High, n(%)		
	QTP 400 mg (N=73)	QTP 800 mg (N=74)	Placebo (n=75)	QTP 400 mg (n=95)	QTP 600 mg (n=98)	Placebo (n=90)
Fasting glucose (mg/dL)	1 (1.5)	0	0	0	1 (1.2)	0
Total Cholesterol (mg/dL)	2 (3.3)	0	1 (1.6)	0	3 (3.5)	1 (1.3)
Triglycerides (mg/dL)	5 (8.9)	1 (1.8)	1 (1.7)	6 (7.5)	12 (14.3)	4 (5.7)
Prolactin (ng/ml)	1 (2.4)	3 (7.5)	1 (2.8)	12 (15.8)	10 (12.3)	2 (2.6)

In study 112, only one female patient in the QTP group had a potentially clinically significant shift in prolactin to 131.5 ng/ml; 3 males had shifts to high prolactin with the highest value was 40.9 ng/ml. In study 149, 8 female patients had increased prolactin in the QTP group compared to none in the placebo.

Comment: The Division also requested that the sponsor conduct an analysis of all clinical trials to study the effects of QTP IR and XR on these safety signals. The sponsor has recently submitted these data for both pediatric and adult population. Further modifications to product labeling will be made based on our review of these submitted data (refer to separate metabolic reviews).

### Body Weight and Growth

In Studies 112 and 149, quetiapine was associated with a significantly greater mean increase in weight and height compared to placebo. In study 112, the increases in body weight for QTP IR 400 mg and 800 mg/day groups were 1.9 and 1.5 Kg, respectively, as compared to a decrease of 0.1 Kg in the placebo group. Since study 112 was an international trial, the Sponsor did provide a separate summary table for mean change in weight for the different pooled geographic locations. For the USA sites, the change from baseline to final visit was +2.7 kg (quetiapine 400 mg, n = 20), +2.0 kg (quetiapine 800 mg, n = 22) and -0.2 kg (placebo, n = 25). In study 149, the increase in body weight for QTP IR 400 mg and 600 mg/day group was 1.7 kg as compared to a 0.4 Kg in the placebo group.

The pooled outlier analysis for studies 112 and 149 showed 17% (57/335) of patients in the quetiapine group gained  $>7\%$  weight compared to 2.5% (4/163) of patients in the placebo group. In Study 112, 23.2% of patients in the quetiapine 400 mg/day group, 18.2% of patients in the quetiapine 800 mg/day group and 6.8% of patients in the placebo group had a  $> 7\%$  weight gain at Day 42. In Study 149, 14.5% of patients in the quetiapine 400 mg/day group, 9.9% of patients in the quetiapine 600 mg/day group and 0% patients in the placebo group had a  $> 7\%$  weight gain at Day 21.

#### 5.2.2.3 Neutropenia and Agranulocytosis

The mean change analyses of hematology parameters did not reveal any new significant findings. Consistent with adult clinical data, a decrease in neutrophil count was noted in both studies,

although the findings in study 149 were similar to placebo. There was similar percentage of shifts to low ANC at anytime ( $< 1.5 \times 10^9/L$ ) in the QTP (4.8%, 14/294) and the placebo groups (3.5%, 5/144). It should be noted that the Division has recently revised Seroquel labeling language under Warnings/Precautions, a subsection entitled “Leukopenia, Neutropenia and Agranulocytosis.”

#### **5.2.2.4 Vital Sign and ECG Changes**

As noted by Dr. Alfaro in her clinical review, the mean change analyses for blood pressure and pulse revealed an increase in supine and standing pulse and systolic and diastolic blood pressure in the pediatric patients treated with quetiapine compared to placebo. In the short-term placebo-controlled studies of 3 to 6 weeks, significantly greater percentages of patients exhibited shifts to systolic blood pressure ( $\geq 20$  mm Hg) in the quetiapine group (15.2%) as compared to placebo (5.5%). Similarly, an increase in the incidence for diastolic blood pressure ( $\geq 10$  mm Hg) was also observed; 40.6% for QTP IR and 24.5% for placebo. No overall effect consistent with orthostatic hypotension was noted in these pediatric trials.

In the 6 week schizophrenia trial in adolescents (Study 112), tachycardia ( $> 110$  bpm) occurred in 5.2% of patients receiving QTP 400 mg and 8.5% of patients receiving QTP 800 mg compared to 0% of patients receiving placebo. Mean increases in heart rate were 3.8 bpm and 11.2 bpm for QTP 400 mg and 800 mg groups, respectively, compared to a decrement of 3.3 bpm in the placebo group.

In the 3 week bipolar mania trial in children and adolescents (Study 149), tachycardia ( $> 110$  bpm) occurred in 1.1% of patients receiving QTP 400 mg and 2.4% of patients receiving QTP 600 mg compared to 0% of patients receiving placebo. Mean increases in heart rate were 12.8 bpm and 13.4 bpm for QTP 400 mg and 600 mg groups, respectively, compared to a decrement of 1.7 bpm in the placebo group.

It should be noted that approximately 11-19% of patients took concomitant psychostimulants in the bipolar study 149 (comorbid ADHD). However, psychostimulants were not allowed in the schizophrenia study 112 but there were similar findings between the two studies with regard to vital sign changes in the population studied.

For detail, I would refer to Tables 60, 61, 62, 63, 69 and 70 of Dr. Alfaro’s clinical review.

Comment: The sponsor has proposed to describe the BP outlier data from pediatric trials in the Warning section, subsection (b)(4) of the labeling (submitted as CBE labeling supplement under SLR-048). I agree with Dr. Alfaro that we should move this subsection up following the orthostatic hypotension subsection. I also agree with Dr. Alfaro that the increased heart rate data from pediatric trials should be included as part of the labeling section 6 under Vital Signs and Laboratory Values subsection.

#### **5.2.2.5 Extrapyramidal Symptoms (EPS) and Tardive Dyskinesia (TD)**

The overall incidence of adverse events consistent with EPS was higher in the quetiapine groups compared to placebo in study 112. In Study 149, the overall rate of EPS was lower in study 149. Specifically, the proportions of patients with adverse events consistent with EPS were 12.3% and 13.5% in the quetiapine 400 and 800 mg as compared to 5.3% in placebo for study 112; 4.2% and 3.1% in the quetiapine 400 and 600 mg as compared to 1.1% in placebo for study 149.

The majority of patients remained in no change category in terms of categorical change from baseline to end of study in Simpson Angus Scale, Barnes Akathisia Scale Global Assessment and AIMS among the treatment groups except for a slightly higher percentage shift to the worsened category (defined as  $\geq 1$  change in total score) in the QTP groups as compared to placebo in study 112. I would refer to Table 38 in Dr. Alfaro's clinical review for detail.

No reported cases of TD in the short-term and the longer-term pediatric studies.

#### **5.2.2.6 Treatment-Emergent Depression**

An analysis of treatment-emergent mania depression was assessed for study 149 (defined as a CDRS-R Children's Depression Rating Scale-Revised total score  $> 40$  at Day 21). The incidence of emergent depression was 2.1% in the quetiapine 400 mg/day group, 1.0% in the quetiapine 600 mg/day group and 3.3% in the placebo group.

#### **5.2.2.7 Suicidality Assessment**

A Columbia-type suicidality assessment (similar to the Columbia-type assessment) was conducted for these clinical trials. The pooled analysis of Studies 112 and 149 showed no significant difference between the drug and placebo groups: five (1.5%) patients experienced suicidal behavior/ideation in QTP compared to 0 in the placebo groups.

#### **5.2.2.8 Cataracts**

A slit-lamp examination by an ophthalmologist was to be performed at entry into the open-label extension study (Study 150) and at the end of this 26-week study. The Sponsor provided these data as categorical shifts in eye examination (normal to abnormal) in the submission. For patients who received placebo in Studies 112 and 149 and then received open-label quetiapine in Study 150, 2/129 (6.3%) had a shift from normal to abnormal eye examination (5 patients had abnormal eye exam at baseline that remained in this category). For patients who received quetiapine in Studies 112 and 149 and then received open-label quetiapine in Study 150, 1/251 (1%) had a shift from normal to abnormal eye examination while 15 patients had abnormal eye exams at baseline that remained in this category.

#### **5.2.3 Conclusion Regarding Safety Data**

This submission revealed no findings which were attributable to Seroquel treatment and inconsistent with the previously observed safety profile of quetiapine IR and XR. Overall, there are no new safety concerns that would preclude an approval action.

### **6.0 WORLD LITERATURE**

The sponsor has indicated that they conducted an update to previously submitted literature search in October 2007 for the annual PSUR regarding published articles pertaining to quetiapine and pediatric patients. They reported that the findings were consistent with the known safety of Seroquel in adults and the safety profile discussed in the proposed labeling.

## **7.0 FOREIGN REGULATORY ACTION**

The sponsor reported that neither seroquel nor seroquel XR has been approved for the treatment of schizophrenia in adolescents or bipolar mania in children and adolescents in any other country. The sponsor also reported that they do not intend to obtain these indications in pediatric patients in the EU as the CHMP/EMA indicated to the sponsor that the clinical program designed for the Written Request would not meet EU Guidelines for clinical investigation of both treatment indications and would not support approval of these pediatric indications in Europe.

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

This set of NDA supplements was included in part of discussion at the PDAC meeting on June 9 and 10, 2009 along with other two atypical antipsychotic drugs for pediatric indications in schizophrenia and bipolar.

The committee's discussion included diagnostic consideration regarding phenomenology of pediatric bipolar mania, comorbid ADHD and concomitant stimulant use, and effect size and adverse events observed in bipolar mania in children and adolescents aged 10 to 17 yrs. Pediatric bipolar disorder can be reliably diagnosed yet has no generally accepted definition regarding the periodicity/episodicity of mania symptoms. The committee feels that the sponsor had made an acceptable case for seroquel's efficacy and safety on schizophrenia in adolescents. The majority voted for "yes" on the efficacy question for both schizophrenia and bipolar mania indications (17 yes; 1 no; no abstention). Regarding the safety question of whether or not seroquel had been shown to be effective and reasonably safe for schizophrenia, the votes were 16 yes, 0 no, 2 abstention; and for bipolar mania, 13 yes, 0 no and 5 abstention.

## **9.0 DSI INSPECTIONS**

Two sites for each indication were selected for inspection: Site 240 (Clinical Investigator Kozlova in Russia) and Site 024 (Dr. Wamboldt from Denver, CO) for Study 112; and Site 019 (Dr. Rease from Riverside, CA) and Site 024 for Study 149. The Russian site was selected because if any significant deficiencies were found, removal of data from this site would yield negative efficacy results for the low dose group and marginally positive results for the high dose group in Study 112. The other sites inspected were chosen because they were large enrolling sites. Despite some inspection deficiencies noted at site 024, the DSI clinical inspection summary did not indicate any data integrity issues. DSI concludes that data from all of these sites appear acceptable for use in support of the proposed indications.

## **10.0 LABELING AND ACTION LETTER**

### **10.1 Final Draft of Labeling Attached to the Action Package**

The sponsor's proposed language has been modified. We should be negotiating labeling changes with the sponsor prior to approval of these NDA supplements.

## 11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that Seroquel is efficacious and reasonably safe in the acute monotherapy treatment of schizophrenia in adolescents and bipolar I disorder, mania in children and adolescents aged 10-17 yrs. (b) (4)



I recommend the Division should consider approval of this set of NDA supplements provided that an agreement is reached between the sponsor and the Agency regarding the language in the labeling.

Cc: HFD-130/Laughren/Mathis/Alfaro/Updegraff

File: NDA/Memo\_N22047\_S045\_046\_082009.doc

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 20639	SUPPL 45		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 46		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M

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NI A KHIN  
08/13/2009

## CLINICAL REVIEW - ADDENDUM

Application Type	NDA
Application Number(s)	020-639 SE5-045, SE5-046
Priority or Standard	P (pediatric)
Related NDAs	020-639 SLR 048 022-047 SLR 022 (Seroquel XR)
Submit Date(s)	10/28/2008
Received Date(s)	10/28/2008
PDUFA Goal Date	4/28/09
Division / Office	Division of Psychiatry Products
Reviewer Name(s)	Cara Alfaro, Clinical Analyst
Addendum Completion Date	8/10/2009
Established Name	Quetiapine fumarate
Trade Name	Seroquel
Therapeutic Class	Antipsychotic
Applicant	AstraZeneca
Formulation(s)	Oral immediate release tablet
Dosing Regimen	Titration to 400 – 800 mg/day for schizophrenia Titration to 400 – 600 mg/day for bipolar I mania
Indication(s)	Schizophrenia, Bipolar I Mania
Intended Population(s)	Adolescents (13 to 17 years) for schizophrenia Children (10 to 17 years) for bipolar I mania

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## **1 Recommendations/Risk Benefit Assessment**

The Sponsor submitted two pivotal trials to support the following pediatric indications “treatment of schizophrenia in adolescents (13 to 17 years of age)” and “treatment of bipolar I mania in children and adolescents (10 to 17 years of age)”.

Several requests for information were pending at the time the clinical review was finalized. This addendum includes a review of this additional data.

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

The Sponsor has adequately responded to additional requests for information and the submitted data does not alter the overall efficacy or safety profile for quetiapine in the child/adolescent population for the treatment of bipolar I mania or for adolescents for the treatment of schizophrenia.

This reviewer recommends an approval action for these supplements, pending finalization of product labeling.

### **1.2 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

The Sponsor has submitted a Medication Guide that adequately addresses key safety issues with quetiapine (e.g. metabolic adverse effects). OSE has been consulted to determine whether any additional REMS are necessary.

### **1.3 Recommendations for Postmarket Requirements and Commitments**

No recommendations for postmarket requirements or commitments.

## **2 Additional Requests for Information**

During the NDA review, this reviewer requested additional information from the Sponsor. The Sponsor formally submitted the responses to the Division on June 16, 2009.

### **2.1 Adverse Events - Sedation and Somnolence**

Request: For Studies 112 and 149, please combine the somnolence and sedation adverse events into one term “somnolence” and recalculate the frequencies for this combined adverse event.

The Sponsor submitted the following frequencies for the combined adverse event “somnolence and sedation”:

Study 112 (schizophrenia): quetiapine 400 mg/day 32.9%, quetiapine 800 mg/day 35.1% and placebo 10.7%. Study 149 (bipolar disorder): quetiapine 400 mg/day 49.5%, quetiapine 600 mg/day 57.1% and placebo (14.4%)

The pooled frequencies for studies 112 and 149: quetiapine 45.0% and placebo 12.7%

## 2.2 Clinical Sites in Germany

Request: In one of the lists of principal investigators tables, there are 6 sites in Germany that participated in study 112 (sites 380, 381, 382, 383, 384, 386). However, only one site (386) enrolled 1 subject in study 112. Was there difficulty in recruiting subjects for this trial in Germany, or is there another reason for the lack of enrollment?

The Sponsor indicated that originally, the health authority in Germany did not want to approve a study with a placebo arm in pediatric patients with schizophrenia. Once the health authority approved the study design, the sites in Germany initiated enrollment – however, enrollment was poor for the following reasons: protracted physicians strike, parent’s unwillingness to allow their children to participate due to the placebo arm, inability to obtain consent from both parents (as required in Germany), patient population more difficult to access than anticipated, late entry of sites into the trial allowed limited time to recruit before enrollment ended.

## 2.3 Vital Signs

Request: Please provide some rationale for the increases in blood pressure (systolic and diastolic) observed in the child/adolescent populations in studies 112 and 149 - this is in contrast to the orthostatic signal present in the adult population.

In their response, the Sponsor was unable to provide a rationale for the increases in blood pressure noted in the child/adolescent populations noting “these findings are distinct from those previously reported for adults, where increases in heart rate have been reported but no important changes in blood pressure have been observed. The precise reasons for these differences are unclear”.

During the Psychopharmacological Drugs Advisory Committee meeting, held June 9-10 2009, the Sponsor indicated that the finding was unexpected. The Sponsor did state that, although the pharmacokinetics of quetiapine are similar between adults and children/adolescents, there are some differences in PK parameters for quetiapine metabolites. The PK study performed in children/adolescents (Study D1441C00028) found that AUCs for quetiapine sulfoxide and N-desalkyl quetiapine metabolites were 27% and 45% higher, respectively, in children/adolescents than in adults. During the Psychopharmacological Drugs Advisory Committee the Sponsor commented that some of these metabolites possess different binding affinities to alpha 1 adrenergic receptors such that this PK difference could potentially explain these blood pressure findings.

Request: In the recent CBE submission, data for increases in blood pressure were summarized for the bipolar and schizophrenia studies in children and adolescents. It appears that these data were pooled across all doses and studies 112 and 149. Please provide a table similar to Table 64 of the clinical study report for study 149 for these data and clarify whether the systolic and diastolic blood pressure changes in labeling refer to supine or standing measurements. Were the data in labeling based on the type of data presented in Table 64? Please provide these data by age group as well (10 - 12, 13-17 yrs.) for study 149.

The Sponsor indicated that the table that included the blood pressure data that they had summarized in the CBE was from Table SA-14 in the summary-clin-safety document in the NDA submission. This table also included these data by age cohort (10-12 and 13-18 yrs.). Please refer to the clinical review for further discussion of blood pressure data.

Request: Please provide a table similar to SA14 (summary-clin-safety) for standing vital sign shifts.

Table SA14 in the summary-clin-safety document in the NDA submission was a table of supine vital sign shifts to clinical importance at any time for pooled studies 112 and 149. Table SA-14 summarized *supine* blood pressure data for shifts to clinical importance at any time. Cut-off values for specific variables included pulse > 120 bpm, pulse  $\geq$  15 bpm increase, systolic blood pressure  $\geq$  20 mmHg increase, diastolic blood pressure  $\geq$  10 mm Hg increase and  $\geq$  20 mm Hg increase and specific cut off increases in systolic blood pressure and diastolic blood pressure according to gender and age.

A review of *standing* vital sign shifts to clinical importance at any time revealed essentially similar frequencies for these outlier values compared to the supine blood pressure data. The only notable difference was in the pulse > 120 bpm category where a higher percentage of quetiapine-treated subjects exhibited a shift in standing pulse compared to supine pulse (see Tables 1 and 2).

Table 1. Standing and Supine Pulse Shifts to > 120 bpm at Any Time

	Quetiapine (N = 340)	Placebo (N = 165)
Supine pulse > 120 bpm	8.1%	0
Standing pulse > 120 bpm	29.5%	0.7%

Source: Table SA-14 in NDA submission and 6/16/09 submission

Table 2. Standing and Supine Pulse Shifts to > 120 bpm at Any Time, By Age Cohort

	Quetiapine 10-12 yrs. (n = 85)	Placebo 10-12 yrs. (n = 36)	Quetiapine 13-18 yrs. (n = 255)	Placebo 13-18 yrs. (n = 129)
Supine pulse > 120 bpm	1.2%	0	10.5%	0
Standing pulse > 120 bpm	25.9%	0	30.8%	0.8%

Source: Table SA-14 in NDA submission and 6/16/09 submission

In their response, the Sponsor stated that “standing BP data are not considered helpful in the interpretation of BP changes and/or the assessment of hypertension status in children, particularly if collected after maneuvers used to elicit orthostatic changes” and that normative standards are derived from sitting BP pressure data...”. I agree with both of these statements and agree that the sitting data, as included in the most recent CBE, is sufficient to summarize these data. Though there were some differences by age cohort, there were small numbers of children (10-12 yrs) enrolled such that an overall summary of effects of quetiapine on vital signs in children/adolescents is appropriate.

Request: For Studies 112 and 149, please provide the subject identifiers for subjects with shifts to high in vital sign parameters (pulse, blood pressure) and provide listings for all study vital sign readings (including unscheduled visits) for these subjects including vital signs obtained in Study 150 for those subjects who continued in the open-label extension study. Did any subjects require treatment with antihypertensive medications?

The listing was reviewed and no pattern for vital signs emerged – sometimes abnormalities persisted into the open label protocol and sometimes they appeared to resolve (no data regarding doses, clinical presentation [e.g. presence of agitation] or other concomitant medications was provided or requested, so these are additional variables).

The Sponsor provided a listing of all patients receiving medications classified as antihypertensives. Some patients received medications for akathisia or ADHD that were classified as antihypertensives (e.g. propranolol, atenolol, clonidine). One 14 YOM patient (b) (6) was taking atenolol for hypertension prior to the study and continued throughout the study, though, notably, the dose was increased from 50 mg/day to 200 mg/day with the addition of other concomitant antihypertensives (irbesartan, ramipril, clonidine). Most of these changes in hypertensive medications were made during the open-label extension phase of the study. A listing of vital signs and concomitant antihypertensive medications for this patient is in the Appendix.

Of note, this listing did not include Patient (b) (6) who experienced a hypertensive crises and was treated with enalapril (this patient was included in the SAE summary of the NDA).

Vital signs were reviewed to evaluate the overall magnitude of increases in supine pulse, systolic blood pressure and diastolic blood pressure. One of the criteria for a clinically important increase in supine pulse was > 120 bpm. Data summaries in the NDA indicated that 27 (8.1%) of quetiapine-treated patients had increases in supine pulse > 120 bpm at any time in the clinical trials (112 and 149). A review of the vital sign listings could only identify ~10 patients who met this criterion. The majority of patients meeting this criterion had elevations in supine pulse in the 120s, only two patients had an increase to 130 bpm.

For supine systolic blood pressure, the definitions for clinically important increases were dependent on age and gender: boys (10-12 yrs) > 123 mmHg; girls (10-12 yrs) > 121 mmHg; boys (13-17 yrs) > 136 mmHg; girls (13-17 yrs) > 128 mmHg. This reviewer arbitrarily chose a cut-off of 130 mmHg to evaluate the magnitude of increase in systolic blood pressure. Fifty-six (~18%) quetiapine-treated patients and 18 (12%) placebo-treated patients had a supine systolic blood pressure > 130 mmHg at one time during the clinical trials. Approximately 25% of patients with this elevation in supine SBP had elevated SBP at baseline. For the quetiapine-treated patients, the majority (~70%) of elevations were ≤ 140 mmHg. For the 4 quetiapine-treated patients and 1 placebo-treated patient who had SBP > 150 mm Hg, listing of vital signs is in the Appendix.

Table 3. Frequency of Supine SBP > 130 mmHg At Any Time – Studies 112 and 149

	Quetiapine	Placebo
N	56	18
130 – 135 mmHg	28 (50%)	12 (67%)
136 – 140 mmHg	11 (19.6%)	4 (22.2%)
141 – 145 mmHg	8 (14.3%)	-
146-150 mmHg	5 (8.9%)	1 (5.5%)
> 150 mmHg	4 (7.1%)	1 (5.5%)

Source: Vital Signs database in NDA and 6/16/09 submission

For supine diastolic blood pressure, the definitions for clinically important increases were also dependent on age and gender: boys and girls (10-12 yrs) ≥ 78 mmHg; boys (13-17 yrs) ≥ 85 mmHg; girls (13-17 yrs) ≥ 82 mmHg. This reviewer arbitrarily chose a cut-off of 90 mmHg to evaluate the magnitude of increase in diastolic blood pressure. Seventeen (5.4%) of quetiapine-treated and 4 (2.6%) placebo-treated patients had increases in supine DBP ≥ 90 mmHg at any time in studies 112 and 149. The majority of these readings were 90 mmHg and were not sustained elevations. The two highest readings in the quetiapine-treated group were elevations to 110 and 112, the latter was a one time elevated reading and the former appeared to be more of a sustained elevation (see vital signs listing in Appendix).

## 2.4 Narratives

Request: Please provide more details regarding the following serious adverse events and adverse events leading to discontinuation:

Study 149: Patient (b) (6) - Tachycardia, Blood Pressure Increased

The narrative indicates that the patient experienced these adverse events on Day 5 - however, the vital signs listing does not provide vitals obtained on Day 5. Please provide these data and any other additional vital sign readings obtained for this patient.

The Sponsor provided a listing of all vital signs.

Study 150: Patient (b) (6) - Pulmonary Hypertension

The narrative indicates that the patient was referred to a pediatric cardiologist. Please provide the consult and pertinent follow-up for this adverse event. Did the event resolve spontaneously after quetiapine was discontinued, did the patient receive any medical treatment for the condition?

Treatment was discontinued on the day of the adverse event of pulmonary hypertension (Day 120). Left ventricular enlargement and sinus arrhythmia were seen on ECG. A 2D echocardiogram was performed and revealed mild pulmonary arterial hypertension and mild tricuspid regurgitation. A chest x-ray and ABG were requested and were normal. Pulmonary artery hypertension, mild-moderate, with estimated PAP of 58 mmHg by pulmonary acceleration time and 46 mmHg by TR jet. Normal-sized pulmonary arteries. Conclusion: pulmonary artery hypertension, mild-moderate. Tricuspid regurgitation, mild. Pulmonary regurgitation, trivial. No further information was provided regarding medical treatment for this condition. The event was reported as resolved on Day 137.

Study 150: Patient (b) (6) - Hypertensive Crisis

It appears that this patient had high blood pressure during the trial (narrative indicates from day 32 - 212) and enalapril is noted as a concomitant medication. Was enalapril initiated during the trial for high blood pressure? Listing 12.2.9.1 does not indicate high blood pressures for the visits included in the listing and the hypertensive crisis value (150/95) is not included in the listing. Please provide all blood pressures obtained for this patient. Did the patient receive any additional treatment for the 150/95 reading? Please provide more clinical details regarding the hemorrhagic rash experienced by this patient.

The Sponsor indicated that enalapril was initiated during Study 150 for high blood pressure. Enalapril was initiated on (b) (6) for increased blood pressure, the SAE of hypertensive crises occurred on (b) (6). The patient was hospitalized for the event for 5 days. Patient was treated with diazepam and bendazol without recurrence of high blood pressure. Event resolved within one day without interruption of study drug. Medical records were never obtained so additional details, including the relevant vital signs, are unknown.

On (b) (6), the patient developed a rash on his skin that was negative for rubella antibodies. The hemorrhagic rash was moderate in intensity and nonserious and resolved within a week.

Study 150: Patient (b) (6) - Suicide attempt

Please provide details regarding the suicide attempt - there is no information provided in the narrative. It is noted that this patient also experienced neutropenia with an ANC = 0.46 on Day 85. WBCs were obtained on Days 89 and 96 but, remarkably, no ANCs were obtained for these days. The next available ANC is at Day 169 (resolution). If the value of 0.46 is correct, why was this patient not discontinued? Please comment.

The Sponsor did not provide any details regarding the suicide attempt.

The Sponsor did acknowledge that ANCs were not obtained on Days 89 and 96 but did comment that the WBCs were in the normal range.

Since there can sometimes be a disconnect in WBC and ANC – e.g. WBC within normal range with low ANC, these ANC counts should have been obtained in this reviewer's opinion.

Study 150: Patient (b) (6) - Syncope

The narrative notes that the patient also experienced the non-serious event "fall (mild intensity and considered related to study medication) Day 1 Day 20". Does this mean that the patient experienced falls from Day 1 to Day 20? Please clarify and provide additional information.

The patient experienced a "fall" sometime between (b) (6) and (b) (6) – the Sponsor indicated that this usually occurs when a patient reports the event and cannot remember the exact date of the event. The dates for the event on the CRF reflect one fall that occurred within that timeframe.

## 2.5 ANC Clarification

Request: Please clarify the absolute neutrophil counts that are sporadically listed in Listing 12.2.8.2.2 (Study 150). On page 919, patient (b) (6) had a WBC count of 5.9 with 25% neutrophils which should be an ANC of 1.47. However, it appears that the ANC listed in the appropriate column indicates a value of 0.18. Please clarify.

Due to a coding error in the database, bands (absolute) were entered in the column "NEUTROPHILS PART.CONC." for listing 12.2.8.2.1. The ANC is 1.48 (x10E9/L).

## 2.6 Rapid-cycling Bipolar Disorder

Request: For Study 149, the inclusion criteria indicate that patients with rapid cycling bipolar disorder could be enrolled. How many patients with rapid cycling bipolar disorder were enrolled? If sufficient numbers were randomized, please perform a separate efficacy analysis for patients with and without rapid cycling bipolar disorder.

The Sponsor indicated that a total of 80 patients with rapid cycling bipolar disorder were included in Study 149, this represented 28% of the study population. The numbers of rapid cycling bipolar disorder subjects randomized to each treatment were n = 18 in the placebo group, n = 25 in the quetiapine 400 mg/day group and n = 18 in the quetiapine 600 mg/day group. The YMRS total score change from baseline to Day 21 was not significant in the rapid cycling subpopulation, however, this is likely due to the smaller numbers in the rapid cycling group as well as a greater mean change from baseline in the placebo group compared to the nonrapid cycling group (Tables 4 and 5). In general, the LS mean changes for the quetiapine groups in both the rapid cycling and nonrapid cycling subgroups were similar with a ~13 – 16 unit decrease in the YMRS total.

Table 4. YMRS Total Score Change From Baseline to Endpoint (Day 21) – **Rapid Cyclers**

	Baseline		Change from Baseline		LSMean Change	LSMean Difference	P-value
	Mean	SD	Mean	SD			
Quetiapine 400 mg	28.9	7.85	-17.4	6.78	-16.45	-4.94	0.072
Quetiapine 600 mg	29.1	6.36	-13.7	10.69	-13.63	-2.13	0.502
Placebo	32.0	5.72	-12.0	11.95	-11.51		

Source: 6/16/09 submission,

Table 5. YMRS Total Score Change From Baseline to Endpoint (Day 21) – **Nonrapid Cyclers**

	Baseline		Change from Baseline		LSMean Change	LSMean Difference	P-value
	Mean	SD	Mean	SD			
Quetiapine 400 mg	29.4	4.87	-14.3	9.01	-13.18	-5.06	0.004
Quetiapine 600 mg	29.3	5.88	-16.4	8.86	-16.18	-8.06	< 0.001
Placebo	29.1	5.15	-9.3	9.51	-8.13		

Source: 6/16/09 submission,

## 2.7 BID vs. TID Dosing

Request: What % of patients received BID and TID dosing in studies 112 and 149? Was any analysis performed regarding overall tolerability (AE incidence, etc.) between these two dosing regimens?

A total of 47 (16.6%) of patients received TID dosing in Study 149 and a total of 33 (14.9%) of patients received TID dosing in Study 112.

In general, the frequencies of adverse events were similar between the BID and TID dosing schedules with few exceptions. The following adverse event frequencies were higher with the TID dosing regimen compared to the BID dosing regimen: akathisia, dizziness, dry mouth, fatigue, increased appetite, nasal congestion, nausea, sedation, somnolence and tachycardia (Tables 6 and 7). There were no significant increases in adverse event frequencies in the BID schedule compared to the TID schedule.

Table 6. Adverse Events By BID or TID Status - Study 112

	Dosing Schedule	Quetiapine 400 mg (N = 147)	Quetiapine 800 mg (N = 74)	Quetiapine Total (N = 147)	Placebo (N = 75)
Total	BID dosing, n (%) TID dosing, n (%)	60 (82.2%) 13 (17.8%)	60 (81.1%) 14 (18.9%)	120 (81.6%) 27 (18.4%)	69 (92.0%) 6 (8.0%)
Akathisia	BID TID	3.3% 7.7%	1.7% 14.3%	2.5% 11.1%	2.9% -
Dizziness	BID TID	6.7% 15.4%	13.3% 21.4%	10.0% 18.5%	4.4% 16.7%
Dry mouth	BID TID	5.0% -	6.7% 21.4%	5.8% 11.1%	1.5% -
Increased appetite	BID TID	1.7% 15.4%	5.0% 14.3%	3.3% 14.8%	2.9% 16.7%
Sedation	BID TID	3.3% 15.4%	1.7% 21.4%	2.5% 18.5%	2.9% 16.7%
Somnolence	BID TID	23.3% 46.2%	30.0% 28.6%	26.7% 37.0%	7.3% -
Tachycardia	BID TID	6.7% -	5.0% 21.4%	5.8% 11.1%	- -

Source: 6/16/09 submission

Table 7. Adverse Events By BID or TID Status - Study 149

	Dosing Schedule	Quetiapine 400 mg (N = 95)	Quetiapine 600 mg (N = 98)	Quetiapine Total (N = 193)	Placebo (N = 90)
Total	BID dosing, n (%) TID dosing, n (%)	76 (80.0%) 19 (20.0%)	80 (81.6%) 18 (18.4%)	156 (80.8%) 37 (19.2%)	80 (88.9%) 10 (11.1%)
Dizziness	BID TID	18.4% 21.1%	15.0% 27.8%	16.7% 24.3%	2.5% -
Dry mouth	BID TID	5.3% 15.8%	3.8% 22.2%	4.5% 18.9%	- -
Fatigue	BID TID	11.8% 21.1%	10.0% 5.6%	10.9% 13.5%	5.0% -
Increased appetite	BID TID	7.9% 15.8%	10.0% 5.6%	9.0% 10.8%	1.3% -
Nasal Congestion	BID TID	2.6% 5.3%	3.8% 16.7%	3.2% 10.8%	2.5% -
Nausea	BID TID	4.0% 15.8%	8.8% 16.7%	6.4% 16.2%	3.8% 10.0%
Sedation	BID TID	17.1% 47.4%	22.5% 38.9%	19.9% 43.2%	3.8% 10.0%
Somnolence	BID TID	27.6% 31.6%	26.3% 55.6%	26.9% 43.2%	8.8% 20.0%
Tachycardia	BID TID	4.0% 10.5%	7.5% 11.1%	5.8% 10.8%	- -

Source: 6/16/09 submission

## 2.8 Prolactin

**Request:** For Study 150, please provide a table similar to Table 62 (patients with potentially clinically important high shifts in prolactin) in the clinical study report for Study 149. For this table, please include prolactin concentrations in ng/ml units; table 11.3.7.3.11.2 in the clinical study report for Study 150 provides the prolactin concentrations in mIU/L units.

The Sponsor provided a table summarizing the patients with potentially clinically important high shifts in prolactin at final visit for Study 150 – the open-label extension study. By protocol, the definition of potentially clinically important high shifts in prolactin was > 20 ng/ml for males and > 26 ng/ml for females.

Table 8 gives the distribution of these high shifts in prolactin for double-blind study 149 and open-label study 150 for comparison purposes (study 112 had only one female patient with a shift to 131 ng/ml). The four females with shifts in prolactin to > 50 ng/ml in Study 150 had values of 50.3, 55.8, 56.7 and 75.1 ng/ml. The sponsor table indicates that the shift to 75.1 ng/ml occurred in a female patient receiving concomitant haloperidol, though the dates of concomitant use were not provided.

Table 8. Distribution of Potentially Clinically Significant Shifts in Prolactin Concentration

	Female		Male	
	Quetiapine	Placebo	Quetiapine	Placebo
<b>Study 149</b>				
N	8	0	15	2
> 20 – 25 ng/ml	NA	NA	7 (47%)	1 (50%)
> 25 – 30 ng/ml	2 (25%)	0	3 (20%)	1 (50%)
> 30 – 35 ng/ml	4 (50%)	0	3 (20%)	0
> 35 – 40 ng/ml	1 (12.5%)	0	1 (7%)	0
> 40 – 45 ng/ml	1 (12.5%)	0	0	0
> 45 – 50 ng/ml	0	0	1 (7%)	0
<b>Study 150</b>				
N	9	NA	10	NA
> 20 – 25 ng/ml	NA		2 (20%)	
> 25 – 30 ng/ml	1 (11.1%)		1 (10%)	
> 30 – 35 ng/ml	2 (22.2%)		1 (10%)	
> 35 – 40 ng/ml	1 (11.1%)		0	
> 40 – 45 ng/ml	1 (11.1%)		4 (40%)	
> 45 – 50 ng/ml	0		2 (20%)	
> 50 ng/ml	4 (44.4%)		0	

Source: 6/16/09 submission

**Request:** Please provide mean change in prolactin concentration for studies 112 and 149 only for the subset of patients with normal prolactin at baseline.

The Sponsor provided the requested analysis, as a pooled analysis for studies 112 and 149. These data were requested since the mean changes from baseline in prolactin were very different between the two studies and it was likely that patients in study 112 (schizophrenia) might have had elevated prolactin at baseline which could have obscured the effects of quetiapine on prolactin. In Study 112, both doses of quetiapine were associated with a mean decrease in prolactin concentration. However, in this pooled analysis that included only patients with normal baseline prolactin, a consistent finding of increased prolactin (as was noted in study 149) was demonstrated. Approximately 77% (223/291) of patients with prolactin data had normal baseline prolactin concentrations.

Table 9. Change from Baseline to Endpoint in Prolactin, *Patients with Normal Baseline Prolactin – Study 112 + 149 Pooled*

	Quetiapine 400 mg/day (N = 123)	Quetiapine 600 mg/day (N = 89)	Quetiapine 800 mg/day (N = 46)	Placebo (N = 125)
n	110	77	36	108
Prolactin (ng/ml)	1.95	3.09	2.20	-0.48

Source: 6/16/09 submission

Table 10. Change from Baseline to Endpoint in Prolactin, *All Patients* – Study 112 and Study 149

	Quetiapine 400 mg/day	Quetiapine 600 mg/day	Quetiapine 800 mg/day	Placebo
Study 112	n = 63	NA	n = 60	n = 63
Prolactin (ng/ml)	-10.5	NA	-7.8	-18.2
Study 149	n = 82	n = 86	NA	n = 82
Prolactin (ng/ml)	2.8	1.9	NA	-1.1

Source: Original NDA submission

## 2.10 Ophthalmoscopic Eye Examinations

**Request:** In the clinical study report for Study 150, Table 11.3.8.1.14 includes the categorical shifts in eye examinations from OL baseline. Please provide more detailed information for these cases. Please provide clinical details describing the cases that shifted from normal to abnormal. Please also provide clinical details describing the cases that were categorized as abnormal at OL baseline and that remained abnormal (e.g. were the same/similar abnormalities noted).

The sponsor submitted a table summarizing the normal to abnormal and abnormal to abnormal eye examination findings. The sponsor also indicated that 2 of these cases (b) (6) were not included in the original NDA submission since the baseline eye examination should have occurred on Day 1 of Study 150 whereas these occurred on Days 5 and 10 respectively. Interesting that these particular cases had signals suggestive of cataract formation after the baseline examination – these cases should have been included in the original NDA submission.

According to the protocol for Study 150, slit-lamp examinations were to be performed at entry into the open-label Study 150 and at the end of this study. Since there were no slit-lamp examinations performed in the double-blind studies, little data is available for a baseline examination in the absence of quetiapine therapy (only for those patients who received placebo in the double-blind studies). A total of 6 patients had a change from normal baseline to abnormal post baseline eye examination – only one was suggestive of cataract formation. Eighteen patients had an abnormal baseline and post baseline eye examination and most of the abnormalities were the same for both assessments, the majority being related to myopia. Two of the 18 patients had eye examinations that revealed signals for cataract formation/opacities. None of these patients had a family history of congenital cataracts.

Table 11. Normal to Abnormal Ophthalmoscopic Eye Examinations

Subject	Age at Study Entry, Gender	Baseline Exam	Post Baseline Exam	Clinical Findings
(b) (6)	15 YOF	(b) (6)	(b) (6)	Spasm of accommodation Induration crystalline lens
	NA**			Myopia
	14 YOM			Myopic astigmatism
	15 YOF			Trace subcapsular cataracts - not visually significant
	14 YOM			Myopia
	17 YOM			Myopic astigmatism

Source: 6/16/09 submission and demographic database in NDA submission

\* Patient was not included in original NDA summary table for categorical shift in eye examination

\*\* Could not find patient in demographic or other databases, likely an error in subject number in the 6/16 submission

Table 12. Abnormal to Abnormal Ophthalmoscopic Eye Examinations

Subject	Age at Study Entry, Gender	Baseline Exam	Post Baseline Exam	Clinical Findings
(b) (6)	15 YOF	(b) (6)	(b) (6)	<i>Baseline - myopia Post BL - Pinpoint cataracts both eyes – suggestive of congenital abnormality. Visually insignificant.</i>
	13 YOF			Both exams same finding – right eye cortical focal opacity
	13 YOM			<i>Both exams same finding – ocular lenses showed punctuate opacities – a few in the right lens and fewer in the left lens</i>
	14 YOM			Both exams same finding – myopia
	16 YOF			Both exams same finding – myopia
	16 YOM			Both exams same finding – astigmatism
	17 YOM			Both exams same finding – myopic astigmatism and myopia
	16 YOM			Baseline – astigmatism Post BL – myopic astigmatism
	17 YOF			Both exams same finding – myopia
	17 YOM			Both exams same finding – myopia
	17 YOM			Both exams same finding – myopic astigmatism
	17 YOF			Both exams same finding – myopic astigmatism
	16 YOM			Both exams same finding – myopic astigmatism and myopia
	17 YOM			Abnormalities not specified
	15 YOF			Both exams same finding – myopia and angiodystrophy
	17 YOM			Both exams same finding – pterygium nasal left eye
	16 YOF			Both exams same finding – myopic astigmatism
	17 YOM			Both exams same finding – corneal macula, right eye secondary to trauma; myopic astigmatism

Source: 6/16/09 submission and demographic database in NDA submission

\* Patient was not included in original NDA summary table for categorical shift in eye examination

## 2.11 Vital Signs: Concomitant Psychostimulants

**Request:** For Study 149, please provide an analysis of mean change in vital signs from baseline to final visit (supine and standing pulse, systolic BP and diastolic BP) for patients on concurrent psychostimulants and those not on concurrent psychostimulants. Please also provide an analysis of clinically important shifts at any time in vital signs for these same groups of patients. For patients with the clinically important shifts at anytime, please provide a line listing of all vital signs.

The Sponsor submitted the requested analyses. Pulse rates did appear to be slightly higher in quetiapine-treated patients receiving concomitant psychostimulants compared to those not receiving concomitant stimulants – but it does appear that the majority of the vital signs signals were related to quetiapine therapy (quetiapine vs. placebo comparisons). [Note: psychostimulant dose had to have been stable for  $\geq 30$  days prior to randomization].

Table 13. Mean Change from Baseline in Vital Signs By Concomitant Psychostimulants (Study 149)

	Quetiapine 400 mg/day		Quetiapine 600 mg/day		Placebo	
	- Stimulants (n = 74)	+ Stimulants (n = 19)	- Stimulants (n = 83)	+ Stimulants (n = 12)	- Stimulants (n = 79)	+ Stimulants (n = 11)
Supine pulse [Standing] (bpm)	8.8 [9.1]	9.1 [9.9]	10.2 [10.9]	12.3 [15.3]	-1.6 [0.2]	1.2 [-0.3]
Supine SBP [Standing] (mmHg)	0.4 [1.7]	1.4 [-0.9]	2.0 [0.0]	1.1 [0.3]	-2.3 [0.0]	-1.1 [-0.8]
Supine DBP [Standing] (mmHg)	1.8 [2.7]	0.2 [-2.2]	2.7 [0.3]	1.9 [1.4]	1.2 [-0.2]	-3.8 [2.4]

Source: 6/16/09 submission

Greater percentages of quetiapine-treated patients receiving concomitant psychostimulants had shifts from normal to high supine pulse at any time compared to those quetiapine-treated patients not receiving concomitant psychotropics. Frequencies of shifts from normal to high for supine SBP and DBP were not greater for patients receiving concomitant psychostimulants.

Table 14. Normal to High at Any Time, Supine Vital Signs – By Concomitant Psychostimulants

	Quetiapine 400 mg/day		Quetiapine 600 mg/day		Placebo	
	- Stimulants (n = 74)	+ Stimulants (n = 19)	- Stimulants (n = 83)	+ Stimulants (n = 12)	- Stimulants (n = 79)	+ Stimulants (n = 11)
Supine Pulse	5.4%	10.5%	6.2%	8.3%	0	0
Supine SBP	19.1%	5.9%	11.5%	10.0%	6.0%	9.1%
Supine DBP	16.4%	17.6%	22.9%	11.1%	12.3%	0

Source: 6/16/09 submission

### 3 Labeling

Sponsor proposed labeling has been reviewed and specific recommendations for changes have been suggested using track changes on the labeling document. In general, the major changes suggested include:

The Sponsor had submitted a CBE-30 in December 2008. This CBE included, primarily, safety data from studies 112 (adolescent - schizophrenia) and 149 (child/adolescent – bipolar mania). The Division provided feedback to the Sponsor requesting that the new data be more prominent in placement in labeling (specifically metabolic risks and blood pressure elevations be elevated to WARNINGS and PRECAUTIONS).

## INDICATIONS

In the Division of Psychiatry Products, it is routine that maintenance indications are granted in pediatric populations if a maintenance claim exists for the adult population and efficacy has been demonstrated in an acute study in the pediatric population. Relevant to these particular efficacy claims, Seroquel and Seroquel XR have an adult bipolar maintenance claim but only as adjunct therapy to lithium or divalproex. Only Seroquel XR has a maintenance indication for schizophrenia. Therefore, by extrapolation from the adult clinical data for Seroquel XR, a maintenance indication should be granted for Seroquel for the treatment of schizophrenia in this pediatric population. Similarly, by extrapolation, this same maintenance indication should be granted for Seroquel in the adult population.

## DOSAGE AND ADMINISTRATION

Currently, there are no comments in labeling to indicate that the higher doses in these fixed dose trials did not confer greater efficacy. Addition of "Efficacy was demonstrated with SEROQUEL at both 400 mg and 600 mg; however, no additional benefit was seen in the 600 mg group." [pertains to bipolar claim; doses of 400 mg and 800 mg relevant to schizophrenia claim]. This is consistent with adult dose data in this section.

## WARNINGS AND PRECAUTIONS

### Hyperlipidemia

According to the National Cholesterol Education Program, the cut-off for clinically significant elevations in cholesterol in children/adolescents is  $\geq 200$  mg/dL. Proposed labeling (b) (4). (b) (4). The  $\geq 200$  mg/dL cut-off is also consistent with the data we had requested for the metabolic analysis. The Sponsor will need to recalculate the data for this lower cut-off value and incorporate into product labeling.

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

In proposed labeling, hypertension (an adverse event occurring specifically in this population) is listed as th (b) (4) in this section. I propose moving this up higher in the list, perhaps following orthostatic hypotension (listed 8<sup>th</sup>) since it is a vital signs related significant adverse event. Also recommend inclusion of the one case of hypertensive crises occurring in the open label trial as this adverse event was significant enough to require hospitalization as well as continued treatment with antihypertensives.

### Cataracts

Since a potential cataract signal was noted in the open-label study (appropriate examinations were not included in the acute studies), suggest inclusion of this population in this section "Lens changes have also been observed in adults, children and adolescents during long-term SEROQUEL treatment...".

### Transaminase Elevations

Currently, there is no mention of the pediatric data. Since no elevations  $> 3X$  ULN were noted in the clinical trials, that should be included here for completeness.

## ADVERSE REACTIONS

Somnolence and sedation adverse reactions now combined into one term "somnolence" per prior recommendation of Division.

Addition of potential dose-related differences in the frequency of common adverse events.

Vital Signs and Laboratory Values subsection

There was no child/adolescent data in this section. The heart rate increases noted on ECG should be included since adult data for this parameter is already included in labeling and the data are significant for the child/adolescent populations.



(b) (4)

## 4 Appendices

### 4.1 Vital Signs Listings for Select Patients

Patient treated with antihypertensives for high blood pressure during Study 112:

Quetiapine	(b) (6) 14 YOM			
	SBP	DBP	Pulse	Antihypertensive
Day -7	130	80	80	atenolol 50 mg/d
Day 1	120	70	70	atenolol 50 mg/d
Day 8	115	70	70	atenolol 50 mg/d
Day 15	120	70	80	day 12: increase to atenolol 100 mg/d
Day 22	120	70	85	
Day 28	130	80	84	
Day 36	140	70	92	
Day 43	120	80	78	
OL Week 1	140	60	88	
OL Week 2	120	70	85	
OL Week 3	125	70	78	
OL Week 4	120	80	84	
OL Week 8	130	80	85	Increase to atenolol 200 mg/d, added ramipril
OL Week 12	120	80	80	
OL Week 16	115	70	70	Added irbesartan
OL Week 20	115	70	90	
OL Week 26	120	80	82	

Patients with supine SBP > 150 mmHg at Anytime in Study 149 or 112:

Quetiapine	(b) (6) 15 YOM		
	SBP	DBP	Pulse
Day -2	129	59	59
Day 1	137	65	66
Day 7	<b>165</b>	76	85
Day 14	132	67	88
Day 21	121	63	91
Day 28	133	65	92
Day 36	142	71	107
Day 43	117	54	80

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 Seroquel (quetiapine fumarate)

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Quetiapine	(b) (6) 17 YOM		
	SBP	DBP	Pulse
Day -5	122	64	84
Day 1	136	66	78
Day 8	138	72	67
Day 16	120	76	78
Day 22	120	72	78
Day 29	118	70	72
Day 36	120	68	76
Day 43	<b>151</b>	69	88

Quetiapine	(b) (6) 17 YOM		
	SBP	DBP	Pulse
Day -11	132	72	95
Day 1	135	66	89
Day 9	146	76	102
Day 15	143	70	86
Day 25	120	90	90
Day 35	131	73	108
Day 45	133	58	111
Day 51	<b>159</b>	82	90

Quetiapine	(b) (6) 14 YOM		
	SBP	DBP	Pulse
Day -9	131	75	90
Day 1	134	75	94
Day 9	137	73	105
Day ?	<b>152</b>	88	111
Day 14	142	81	97
Day 23	140	72	98

Placebo	(b) (6) 14 YOM		
	SBP	DBP	Pulse
Day -4	139	66	65
Day 1	131	70	98
Day 7	135	57	85
Day 14	142	58	73
Day 19	133	75	72
Day 26	<b>163</b>	64	64
Day 34	107	57	78
Day 43	135	66	59

Patients with sustained supine DBP > 90 mmHg at Anytime in Study 149 or 112:

Quetiapine	(b) (6) 15 YOM		
	SBP	DBP	Pulse
Day -22	105	65	84
Day -9	105	65	84
Day 1	110	65	88
Day 9	110	70	84
Day 16	110	65	84
Day 23	120	70	82
Day 30	140	<b>100</b>	96
Day 37	130	<b>90</b>	88
Day 43	130	<b>110</b>	86

Clinical Review - **Addendum**  
Cara Alfaro, Pharm.D.  
NDA 020639 SE5-045 and SE5-046  
Seroquel (quetiapine fumarate)

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Quetiapine	(b) (6) 17 YOM		
	SBP	DBP	Pulse
Day -12	130	95	78
Day 1	120	80	76
Day 8	130	90	100
Day 15	150	90	86
Day 22	150	90	96
Day 29	140	90	104
Day 37	140	90	84
Day 43	140	100	86

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 20639	SUPPL 45		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 45		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 45		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 45		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 45		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 45		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 45		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 45		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 45		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 46		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 46		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 46		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 46		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 46		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 46		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 46		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 46		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 48		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 48		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 20639	SUPPL 48		SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA 22047	SUPPL 22		SEROQUEL XR
NDA 22047	SUPPL 22		SEROQUEL XR
NDA 22047	SUPPL 22		SEROQUEL XR

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/s/

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CARA L ALFARO

08/11/2009

NI A KHIN

08/13/2009

I concur with Dr. Alfaro's recommendation that this set of NDA supplements be considered for approval; see memo to file for additional comments.

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	020-639 SE5-045, SE5-046
Priority or Standard	P (pediatric)
Submit Date(s)	10/28/2008
Received Date(s)	10/28/2008
PDUFA Goal Date	4/28/09
Division	Division of Psychiatry Products
Reviewer Name(s)	Cara Alfaro, Clinical Analyst
Review Completion Date	5/11/2009
Established Name	Quetiapine fumarate
Trade Name	Seroquel
Therapeutic Class	Antipsychotic
Applicant	AstraZeneca
Formulation(s)	Oral tablet
Dosing Regimen	Titration to 400 – 800 mg/day for schizophrenia Titration to 400 – 600 mg/day for bipolar I mania
Indication(s)	Schizophrenia, Bipolar I Mania
Intended Population(s)	Adolescents (13 to 17 years) for schizophrenia Children (10 to 17 years) for bipolar I mania

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## **1 Recommendations/Risk Benefit Assessment**

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

The Sponsor has submitted two pivotal trials to support the following pediatric indications “treatment of schizophrenia in adolescents (13 to 17 years of age)” and “treatment of bipolar I mania in children and adolescents (10 to 17 years of age)”.

Related to this submission, and at the request of the Division of Psychiatry Products, the Sponsor submitted data for the effect of quetiapine on several metabolic parameters for adult and pediatric/adolescent subjects in their clinical trials database. The review of the adult metabolic data has been recently completed and the pediatric metabolic data is currently under review.

The Sponsor has also submitted a Changes Being Effected labeling supplement that has incorporated some of the pediatric/adolescent safety data; this labeling supplement is under review.

The efficacy and safety data from the two pivotal trials in the current submission will be presented at a Psychopharmacological Drugs Advisory Committee (PDAC) meeting scheduled for June 9 and 10, 2009.

*Recommendations for regulatory action will be made when all reviews have been completed and all pending requests for additional data and analyses from the Sponsor have been received and reviewed. An addendum to this clinical review is therefore expected and will also include a comprehensive review of proposed product labeling.*

### **1.2 Risk Benefit Assessment**

At the PDAC meeting, the efficacy and safety data for quetiapine (along with other atypical antipsychotics) will be presented and the risks/benefits discussed. Further evaluation of the risk/benefit profile of quetiapine in the treatment of schizophrenia in adolescents and the treatment of bipolar I mania in children and adolescents will occur after this meeting.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

Further evaluation of postmarket risk evaluation and mitigation strategies for quetiapine in the treatment of schizophrenia in adolescents and the treatment of bipolar I mania in children and adolescents will occur after the scheduled PDAC meeting.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Quetiapine (Seroquel®) is a dibenzothiazepine derivative which interacts with a broad range of neurotransmitter receptors including serotonin, dopamine and adrenergic receptors.

Quetiapine has been approved by the FDA for the treatment of schizophrenia, bipolar mania and bipolar depression in adults (see the summary table below).

Table 1. Indication and Date(s) of Approval of Quetiapine Fumarate immediate release (Seroquel) [NDA 20-639]

Indication in Adults	Date of Approval
Schizophrenia (acute treatment)	9/26/1997
Acute Manic Episodes associated with Bipolar I Disorder monotherapy or adjunct therapy to lithium or valproex	1/12/2004
Depressive Episodes associated with Bipolar Disorder	10/20/2006
Maintenance Treatment of Bipolar I Disorder as adjunct therapy to lithium or divalproex	5/13/2008

### 2.2 Currently Available Treatments for Proposed Indications

Two atypical antipsychotic agents, Risperdal (risperidone) and Abilify (aripiprazole) are approved for use in the pediatric population for the treatment of schizophrenia (in adolescents) and bipolar mania (age 10-17 yrs). Lithium is also approved in the treatment of bipolar disorder (age >12 yrs).

### 2.3 Availability of Proposed Active Ingredient in the United States

Quetiapine fumarate (immediate release tablets) was first approved for the acute treatment of schizophrenia in adults on September 26, 1997. Quetiapine is currently available as 200, 300 and 400 immediate-release tablets.

Quetiapine extended release (Seroquel XR) was first approved on 5/17/2007 for the acute treatment of schizophrenia. Seroquel XR is currently available as 50, 150, 200, 300 and 400 mg extended-release tablets.

### 2.4 Important Safety Issues with Consideration to Related Drugs

Atypical antipsychotics have been associated with several safety issues. Among the major safety issues are increased mortality in elderly patients with dementia-related psychosis, clinical worsening and suicidality, neuroleptic malignant syndrome, tardive dyskinesia (TD), orthostatic hypotension, hyperglycemia, weight gain and diabetes mellitus.

The sponsors of atypical antipsychotics have been asked to provide additional data and pooled analyses for the metabolic profile safety signals. This includes AstraZeneca who have been asked to provide data and analyses for quetiapine IR and quetiapine XR for effects on lipids (cholesterol, HDL, LDL, triglycerides), glucose (glucose, HbA1c, UA glucose), and weight for both adults and pediatric subjects (see Division letter January 8, 2008). The Sponsor recently provided these data on 6/26/08. The adult metabolic data review was completed in 03/2009 and

was part of the discussion at the PDAC meeting on 4/8/2009. The pediatric metabolic data are currently under review.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

February 11, 2003	FDA issued a pediatric written request
August 4, 2003	Sponsor requests a meeting with the Division to discuss the pediatric development program. Briefing document submitted which included a request for modifications to the Written Request and clinical study protocols 130, 112, 149 and 150.
November 4, 2003	Meeting between Sponsor and Division regarding pediatric development program. Concurrence on major protocol design issues including dosing and primary endpoints.
May 25, 2004	Protocols for Studies 112, 149 and 150 submitted to IND 32,132
February 3, 2005	The time for submission of reports was extended to 7 years from date of the Written Request letter.
March 29, 2006	Sponsor submitted statistical analysis plan for Study 149
June 19, 2007	Sponsor submitted statistical analysis plan for Studies 112 and 150

## 2.6 Other Relevant Background Information

Neither quetiapine or quetiapine XR have been approved for the treatment of schizophrenia in adolescents or bipolar mania in children and adolescents in any other country. The sponsor did not report any withdrawal of this product in other countries.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

See Sections 3.2 (Compliance with Good Clinical Practices) for other comments regarding data quality and integrity.

This reviewer completed a brief audit of adverse event safety data by comparing case report forms, narratives and line listings for consistency on reporting. Overall, there was good consistency of adverse event information across these sources of data. Adverse event coding (verbatim to preferred terms) appeared to be appropriate. No significant deficiencies were noted.

This reviewer did note that the narratives for serious adverse events and discontinuations due to adverse events were not comprehensive and additional data were requested from the Sponsor. Additionally, line listings (e.g. vital signs) did not include assessments obtained at times coordinating with adverse event reports (e.g. hypertensive crisis) – these discrepancies required further data from the Sponsor.

### 3.2 Compliance with Good Clinical Practices

In order to assess good clinical practice (GCP) compliance, a Division of Scientific Investigations (DSI) inspection for the following clinical investigator sites were requested: Site 240 (Clinical Investigator Kozlova in Russia) and Site 024 (Dr. Wamboldt from Denver, CO) for Study 112; and Site 019 (Dr. Rease from Riverside, CA) and Site 024 for Study 149. The Russian site was selected because if any significant deficiencies were found, removal of data from this site would yield negative efficacy results for the low dose group and marginally positive results for the high dose group in Study 112. The other sites inspected were chosen because they were large enrolling sites. Despite some inspection deficiencies noted at site 024, the DSI inspection summary report dated 4/27/09 concludes that data from all of these sites appear acceptable for use in support of the proposed indications.

The Sponsor received a letter from the FDA on 6/23/08 regarding allegations of research misconduct by John Gilliam, M.D., a clinical investigator who participated in the clinical development programs involving quetiapine and quetiapine XR. The FDA requested that pivotal efficacy trials be reanalyzed excluding patients from Dr. Gilliam's site and to compare this reanalysis to the original analysis. A total of 32 patients were randomized into the two pivotal trials from Dr. Gilliam's site: 6 patients (6/222 = 2.7%) were randomized in pivotal Study 112 and 28 patients (26/284 = 9.2%) were randomized into pivotal Study 149. A reanalysis excluding patients from this site was performed for each pivotal trial and the results were similar to the original analyses (see Section 6.1.1 and 6.2.1).

### 3.3 Financial Disclosures

Form 3455 (version 4/2006) "Disclosure – Financial Interests and Arrangements for Clinical Investigators" was available for the majority of investigators. Only two investigators were identified as having received "significant payments" of  $\geq$  \$25,000 for research funding, consulting fees or honoraria. These investigators included Dr. (b) (6), a subinvestigator at center (b) (6) for Study (b) (6) and Dr. (b) (6), a primary investigator at center (b) (6) for Studies (b) (6). No patients were enrolled in Study (b) (6) at Dr. (b) (6) center. Dr. (b) (6) center enrolled and (b) (6). The number of patients enrolled and randomized into the two pivotal trials at Dr. (b) (6) center are  $<$  5% of the efficacy populations in each study and is unlikely to significantly impact the overall study results.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Julia Pinto, Ph.D., is the CMC reviewer for this set of NDA supplements. All CMC information is cross-referenced to the original NDA. No environmental assessment is provided in this submission. As noted by Dr. Pinto in her review dated 04/16/2009, the EA recommended as FONSI (no significant impact) by Ranan Bloom, Ph.D. dated December 11, 2007 is valid through 2011. From the CMC standpoint, these NDA supplements are recommended for approval.

### 4.2 Clinical Microbiology

Not applicable.

### **4.3 Preclinical Pharmacology/Toxicology**

No new pharm/tox information in this submission.

### **4.4 Clinical Pharmacology**

The Office of Clinical Pharmacology (OCP) reviewer is Kofi Kumi, Ph.D. The OCP review dated 03/12/09 reviewed the data from the pediatric PK study (Study 28). In addition, the OCP-Pharmacometric Team, Hao Zhu, Ph.D., and Christine Garnette, Pharm.D., provided their assessment of QT data from the two pediatric pivotal studies in the same review. They also provided some labeling comments for the clinical pharmacology section.

#### **4.4.1 Mechanism of Action**

The mechanism of action of quetiapine is unknown, but its higher 5HT<sub>2</sub>/D<sub>2</sub> binding ratio may contribute to its antipsychotic and mood stabilizing properties.

#### **4.4.2 Pharmacodynamics**

Quetiapine does not appear to prolong QT<sub>c</sub> interval in children and adolescents at the proposed clinical doses. The potential for QT<sub>c</sub> prolongation was evaluated by the quetiapine concentration – QT<sub>c</sub>F relationship modeling derived from data from a thorough QT study in healthy adults. Based on the assumption that the concentration-QT relationships are similar between the pediatric patients and healthy adults, the model predicted mean placebo-adjusted baseline corrected QT<sub>c</sub> intervals are less than 10 ms following the highest dose tested in the two pivotal pediatric studies (Study 112 and 149). In addition, the largest observed mean QT<sub>c</sub>F interval change from baseline observed in the clinical trial was around 2 ms (i.e., approximately 4 ms difference in study 112 and no difference between the quetiapine and placebo in study 149). No patients had QT<sub>c</sub>F values above 500 ms or mean change from baseline in QT<sub>c</sub>F greater than 60 ms in both pediatric studies.

#### **4.4.3 Pharmacokinetics**

The OCP review of pediatric PK data is summarized. There was a tendency for children (10 -12 years of age) to have higher exposure of quetiapine (AUC 36% – 55% and C<sub>max</sub> 54% - 71% higher) than the levels observed in adolescents (13 to 17 years). Dose normalized exposures were generally lower (AUC = 12% lower and C<sub>max</sub> = 8% lower) in pediatric patients than adults. Dose normalized, weight-normalized AUC and C<sub>max</sub> decreased by about 40% in pediatric population (10 to 17 yrs) when compared to adults. These differences are not expected to be clinically relevant.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 2. Clinical Trials Submitted

Protocol	Study Design*	Patients and Diagnosis	Treatment Arms	Duration of Treatment
D1441C00028 "Study 028" <b>PK Study</b>  Region(s): United States	MC, OL, inpatient	Children and adolescents (10-17 years) with schizophrenia, schizoaffective disorder or bipolar disorder	Quetiapine IR titrated from 50 mg (day 1) up to 800 mg/day over 11 days administered BID.  N = 28 enrolled (n = 27 in safety eval, N = 24 in PK eval)	13 days
D1441C00112 "Study 112" <b>Pivotal Study</b>  Region(s): United States, Poland, Russia, Serbia, Ukraine, India, Malaysia, Philippines, South Africa, Germany	MC, R (1:1:1), DB, PC parallel group study	Adolescent (13-17 years) patients with schizophrenia	Quetiapine IR fixed doses of 400 mg/day and 800 mg/day administered BID or TID; placebo  N = 268 enrolled ITT population: N = 220 Safety population: N = 222	42 days
D1441C00149 "Study 149" <b>Pivotal Study</b>  Region(s): United States	MC, R (1:1:1), DB, PC, parallel group study	Child and adolescent (10 – 17 years) with bipolar mania	Quetiapine IR fixed doses of 400 mg/day and 600 mg/day administered BID or TID; placebo  N = 393 enrolled ITT population: N = 277 Safety population: N = 283	21 days
D1441C00150 "Study 150" <b>Safety Study</b>  Region(s): United States, Poland, Russia, Serbia, Ukraine, India, Malaysia, Philippines, South Africa, Germany	MC, OL, flexible dose study	Patients enrolled from studies 112 and 149	Quetiapine IR flexible dosing target of 400 mg/day to 800 mg/day administered BID or TID (could lower to 200 mg/day based on tolerability)  N = 381 enrolled Safety population: N = 380	26 weeks

\*PK = pharmacokinetics, MC = multicenter, OL = open-label, R = randomized, PC = placebo-controlled

## 6 Review of Efficacy

### **Efficacy Summary**

The sponsor has provided sufficient evidence to support efficacy claims for acute treatment for quetiapine in both schizophrenia in adolescents (13-17 yrs of age) and bipolar mania in children and adolescents (10-17 yrs of age).

The primary efficacy endpoint for the schizophrenia study (Study 112) was the change from baseline to endpoint in the PANSS total score (MMRM analysis). The overall study results were statistically significant for quetiapine 400 mg/day versus placebo (LS Mean Diff = -8.16,  $p = 0.043$ ) and quetiapine 800 mg/day versus placebo (LS Mean Diff = -9.29,  $p = 0.009$ ). The LOCF analysis showed similar results for both quetiapine groups compared to placebo.

The primary efficacy endpoint for the bipolar I mania study (Study 149) was the change from baseline to endpoint in the YMRS total score (MMRM analysis). The overall study results were statistically significant for quetiapine 400 mg/day versus placebo (LS Mean Diff = -5.21,  $p < 0.001$ ) and quetiapine 600 mg/day versus placebo (LS Mean Diff = -6.56,  $p < 0.001$ ). The LOCF analysis showed similar results for both quetiapine groups compared to placebo.

### 6.1 Studies Pertinent to Schizophrenia Claim

#### Rationale for Selection of Studies for Review

The efficacy review was focused on data collected in a single study D1448C00112 (Study 112), which was a 6-week, international, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of quetiapine fumarate (Seroquel) immediate-release tablets in daily doses of 400 mg and 800 mg compared with placebo in the treatment of adolescents (13 to 17 yrs of age) with schizophrenia.

#### 6.1.1 Study 112

##### Clinical Trial

Study 112 [Protocol D1441C00112] "A 6-week, international, multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase IIIb study of the efficacy and safety of quetiapine fumarate (Seroquel) immediate-release tablets in daily doses of 400 mg and 800 mg compared with placebo in the treatment of adolescents with schizophrenia".

This international study was conducted in 46 sites enrolling 268 patients: 23 sites in the United States ( $n = 88$  enrolled), 2 sites in Poland ( $n = 9$  enrolled), 4 sites in Russia ( $n = 40$  enrolled), 4 sites in Serbia ( $n = 31$  enrolled), 3 sites in Ukraine ( $n = 28$  enrolled), 2 sites in India ( $n = 11$  enrolled), 2 sites in Malaysia ( $n = 8$  enrolled), 4 sites in Philippines ( $n = 46$  enrolled), 1 site in South Africa ( $n = 6$  enrolled), 1 site in Germany ( $n = 1$  enrolled).

First patient enrolled 10/1/2004, last patient completed 6/20/2007.

##### Methods/Study Design/Analysis Plan

This study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group 6-week trial in male and female inpatient and outpatient adolescents (age 13 – 17 years) with DSM-IV diagnosis of schizophrenia (confirmed by the K-SADS-PL). Following a medication washout period of 1 to 28 days, patients were

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randomized (1:1:1) to one of three treatment groups: quetiapine 400 mg/day, quetiapine 800 mg/day or placebo. Study medication was administered twice or three times daily per the judgment of the investigator. Quetiapine was titrated to the target fixed dose according to the following regimen:

Table 3. Quetiapine treatment regimens (mg/day) for administration

Dose group	Time	Study day										
		1	2	3	4	5	6	7	8	9	10	11-42
400 mg	AM	NA	50	100	100	200	200	200	200	200	200	200
	PM	50	50	100	200	200	200	200	200	200	200	200
800 mg	AM	NA	50	100	100	200	200	300	300	400	400	400
	PM	50	50	100	200	200	300	300	400	400	400	400

AM Morning. NA Not Applicable. PM Evening.

From Sponsor's Table 5 in Clinical Study Report

According to this titration regimen, target fixed doses were reached by Day 5 (400 mg/day) and Day 9 (800 mg/day). Based on tolerability issues, investigators could administer study drug three times daily. No more than 400 mg was to be administered as a single dose.

For inclusion into the study, patients had to have a PANSS total score  $\geq 60$  at screening and baseline and a score of  $\geq 4$  on at least one of the following items: delusions, conceptual disorganization, or hallucinations (see all inclusion/exclusion criteria in Appendix 9.3).

Allowable concomitant medications included benzotropine for the treatment of emergent EPS, diphenhydramine (up to 50 mg/day) for "sleeplessness", lorazepam (up to 4 mg/day – not to exceed 4 days in any study week) orally or IM for the treatment of agitation or anxiety, propranolol for the treatment of akathisia. The following antidepressants were allowable if ongoing if needed in the clinical judgment of the investigator and if the dose had been stable  $> 30$  days before screening (no adjustments were permitted): bupropion, citalopram, escitalopram, sertraline, or venlafaxine. Psychostimulants were not allowable concomitant medications.

Discontinuation criteria, included discontinuation due to adverse events but also included severe non-compliance to protocol or safety reasons as judged by the investigator or Sponsor; CGI-I score of 6 (much worse) or more at Day 14 or later (patient was to be withdrawn or hospitalized); CGI-I score of 5 (minimally worse) or more at 2 consecutive visits, starting with Day 14 (patient to be withdrawn or hospitalized); a patient who was hospitalized for meeting either CGI-I criteria (as listed previously) and who did not show improvement in the CGI-I score after one week of hospitalization; and patient unable to tolerate the assigned dose of study medication.

Patients completing this study, or were discontinued due to worsening of their symptoms, or were discontinued due to an AE not related to quetiapine were given the option to enter a 26-week, open-label quetiapine study (D1441C00150).

*Efficacy assessments* – also refer to Study Assessments Flow Chart in Appendix 9.4

The primary efficacy assessment was the PANSS total score. Secondary efficacy assessments included Clinical Global Impression (CGI) severity of illness and global improvement items, and Children's Depression Rating Scale-Revised (CDRS-R). No secondary assessments were identified as key secondaries for purposes of inclusion in product labeling.

*Safety assessments*

Safety assessments and variables included:

Physical examination, vital signs, weight, BMI, ECG, laboratory assessments (hematology, chemistry, prolactin).

EPS – Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS) and Abnormal Involuntary Movement Scale (AIMS)

The incidence of anticholinergic medication use to treat treatment emergent EPS

### *Statistics*

The primary outcome variable was the change from baseline to Day 42 in the PANSS total score. The primary analysis was MMRM (unstructured covariance pattern). Baseline PANSS total score was used as a covariate, other variables in the model included treatment, region, visit, and visit-by-treatment interaction. All statistical comparisons used 2-sided tests with a significance level of 0.050, unless otherwise specified. The two contrasts of interest were the 400 mg/day and the 800 mg/day quetiapine groups versus placebo and the Simes-Hommel step-up procedure was used for adjustment of the 2 primary comparisons.

An additional analysis using ANCOVA model with missing values imputed by the LOCF method was conducted to further assess robustness of the primary analysis.

Centers were pooled into three geographically based regions: USA, Central and Eastern Europe including South Africa (Serbia, Russia, Ukraine, Germany, Poland, South Africa), and Asia (India, Malaysia, Philippines).

Sample size determination: A total of 66 evaluable patients per treatment group (N = 198) would provide at least 85% power to detect a difference of 15 points between either the 400 mg/day or 800 mg/day quetiapine treatment group and the placebo group for the mean change from baseline in PANSS total score. A Bonferroni correction using  $\alpha = 0.025$  for each dose was used as a conservative approach for obtaining the sample size estimate. The sample size calculation assumed a SD of 26 and a 2-tailed test at an overall type I error rate of 0.05. An additional 51 (20%) patients were added to provide an estimate of 249 patients needed for screening. These additional patients were added to account for those patients who may be screened but who may not become evaluable.

No interim analyses were planned or performed.

Definitions of the ITT and safety populations were standard. ITT population: all randomized patients who were given study treatment and who had baseline and at least one post-baseline PANSS assessment.

Safety population: all randomized patients who were given study treatment.

## Results

### Demographics

The mean age (15.4 yrs) was similar across the treatment groups. There were more males enrolled (58.6% of the overall study population) with similar proportion in each treatment group. The majority of patients were Caucasian (61%).

Table 4. Patient Demographics

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 73
Gender n (%)			
Male	43 (58.9)	44 (59.5)	42 (57.5)
Female	30 (41.1)	30 (40.5)	31 (42.5)
Age (years)			
Mean	15.45 (1.25)	15.45 (1.34)	15.34 (1.39)
Median	16	16	16
Range	13 - 17	13 - 17	13 - 17
Race n(%)			
Caucasian	45 (61.6)	44 (59.5)	46 (63)
Black	7 (9.6)	9 (12.2)	11 (15.1)
Oriental	15 (20.5)	13 (17.6)	12 (16.4)
Other	6 (8.2)	8 (10.8)	4 (5.5)
Ethnic Group n (%)			
African	1 (1.4)	1 (1.4)	2 (2.7)
African-American	6 (8.2)	8 (10.8)	9 (12.3)
Asian	15 (20.5)	14 (18.9)	10 (13.7)
Chinese	1 (1.4)	1 (1.4)	1 (1.4)
Hispanic	4 (5.5)	5 (6.8)	5 (6.8)
Native American	0	0	1 (1.4)
Not applicable	36 (49.3)	34 (45.9)	32 (43.8)
Other	10 (13.7)	11 (14.9)	13 (17.8)

From Sponsor Table 22 in Clinical Study Report

*Baseline Characteristics*

Select baseline characteristics are listed in Table 5. The treatment groups were well matched with regard to baseline characteristics of diagnosis and severity of illness. Approximately 10% of patients in each treatment group had a comorbid ADHD diagnosis. Baseline body weight and BMI were similar among the groups.

Table 5. Baseline Characteristics

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 73
DSM-IV diagnosis n (%)			
Schizophrenia, disorganized	6 (8.2)	5 (6.8)	5 (6.8)
Schizophrenia, paranoid	53 (72.6)	50 (67.6)	52 (71.2)
Schizophrenia, residual	0	1 (1.4)	0
Schizophrenia, undifferentiated	14 (19.2)	18 (24.3)	16 (21.9)
Comorbid ADHD diagnosis n (%)	7 (9.6)	8 (10.8)	7 (9.6)
Baseline CGI-Severity Score			
Mean (SD)	4.7 (0.77)	4.6 (0.76)	4.7 (0.67)
Range	4 – 7	3 – 6	4 – 6
Baseline PANSS Total Score			
Mean (SD)	96.2 (17.7)	96.9 (15.3)	96.7 (18.0)
Range	46 – 135	69 – 137	60 – 165.5
Years since first known diagnosis of schizophrenia			
Mean (SD)	2.3 (2.3)	2.5 (2.5)	2.2 (1.5)
Total number of schizophrenia hospitalizations [mean (SD)]	1.3 (1.6)	1.1 (1.3)	1.6 (1.9)
Has the subject been hospitalized for a suicide attempt?			
Yes n (%)	2 (2.7)	0	1 (1.4)
Current or prior exposure to quetiapine?			
Yes, n (%)	8 (11)	6 (8.1)	9 (12.3)
Quetiapine average daily dose in mg			
n	8	6	8
Mean (SD)	200 (157.5)	183.3 (132.9)	271.9 (167.7)
Weight (kg)			
Mean (SD)	60.95 (19.1)	61.73 (14.67)	62.78 (14.35)
Range	34-128	36-103	35-113
BMI (kg/m <sup>2</sup> )			
Mean (SD)	21.82 (5.57)	22.46 (4.75)	22.67 (4.72)
Range	14.5-41.3	13.5-37.2	15.4-40

From Sponsor Table 23 in Clinical Study Report, baseline PANSS scores obtained from Table 11.2.1.1.1

### Patient Disposition

A total of 268 patients were enrolled into the clinical trial. Forty-six were screening failures, primarily due to not fulfilling eligibility criteria. A total of 222 patients were randomized and received study drug. One hundred and sixty-four subjects (74%) completed the study. The main reasons for subject discontinuation from the study were adverse events, study-specific discontinuation criteria and patients not willing to continue. Quetiapine groups had higher completion rates (i.e., 76.7% and 82.4% in the 400 mg, 800 mg quetiapine vs. 62.7% in placebo). There were more subjects listed for dropout due to adverse events in the quetiapine treatment groups compared to the placebo group.

Table 6. Patient Disposition

	Quetiapine 400 mg/day	Quetiapine 800 mg/day	Placebo
Randomized	73	74	75
<b>Discontinued Study</b>	<b>17 (23.3%)</b>	<b>13 (18.6%)</b>	<b>28 (37.7%)</b>
Adverse Event	5 (6.8%)	7 (9.5%)	2 (2.7%)
Met discontinuation criteria*	6 (8.2%)	2 (2.7%)	15 (20%)
Patient not willing to continue	3 (4.1%)	3 (4.1%)	8 (10.7%)
Lost to follow-up	0	0	2 (2.7%)
Other**	3 (4.1%)	1 (1.4%)	1 (1.3%)
<b>Completed Study</b>	<b>56 (76.7%)</b>	<b>61 (82.4%)</b>	<b>47 (62.7%)</b>
Enrolled in OL study 150	56 (76.7%)	58 (78.4%)	61 (81.3%)

From Sponsor Figure 1 in Clinical Study Report

\*the majority of these discontinuations were due to lack of efficacy as defined by CGI-I scores per discontinuation criteria. [from Disposition of Each Subject document in submission]

\*\*examples of "other" discontinuations included noncompliance, family withdrew consent, moving out of state, lack of efficacy, "according to agreement with sponsor" [from Disposition of Each Subject document in submission]

Table 7. Sample Sizes for ITT and Safety Populations

	Total	Quetiapine 400 mg/day	Quetiapine 800 mg/day	Placebo
ITT Population	220	73	73	74
Safety Population	222	73	74	75

### Concomitant Medication Use

Allowable concomitant medications but with restrictions included benztropine for EPS, propranolol for akathisia, lorazepam for anxiety/agitation, and diphenhydramine for "sleeplessness".

Select antidepressants were allowed if the dose had been stable for > 30 days prior to screening. Allowable antidepressants included bupropion, citalopram, escitalopram, sertraline and venlafaxine. No dose adjustment was permitted.

Approximately 10% of patients in each treatment group had a comorbid diagnosis of ADHD. The incidence of antidepressant and psychostimulant use during the study is presented. The use of anticholinergic medications for EPS and the use of sleep medication are also presented.

Table 8: Concomitant Medication Use

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 73
“Sleep medication”	19 (26%)	16 (21.6%)	23 (30.7%)
Antidepressants	5 (6.8%)	1 (1.4%)	2 (2.7%)
Psychostimulants	0	0	0
Benzodiazepines			
Alprazolam	2 (2.7%)	0	0
Clonazepam	2 (2.7%)	5 (6.8%)	1 (1.3%)
Diazepam	1 (1.4%)	0	3 (4%)
Lorazepam	13 (17.8%)	8 (10.8%)	15 (20%)
Midazolam	2 (2.7%)	0	0
Diphenhydramine	7 (9.6%)	8 (10.8%)	9 (12%)
Anticholinergics	4 (5.5%)	1 (1.4%)	0

From Sponsor Tables 11.1.7.4, 11.3.15.1, 11.3.20.1, 11.3.13.1

### Important Protocol Violations

The majority of major protocol violations were patients using anxiolytics/hypnotics not specifically permitted or other concomitant medication violations. Concomitant medication use is discussed in the previous section. No other major protocol violations were noted that would impact the overall interpretation of the study results. Of note, though major protocol violations were included in subject discontinuation criteria in the protocol, it does not appear that any patients were discontinued from the study based on this criterion.

### Dosing

The study used two fixed doses of quetiapine, 400 mg/day and 800 mg/day, vs. placebo.

### Efficacy Findings

#### Primary Efficacy Analysis

The MMRM analysis showed both quetiapine 400 mg/day and quetiapine 800 mg/day were statistically significantly superior to placebo.

Table 9. Primary Efficacy Variable (MMRM): PANSS Total Score Change from Baseline to Endpoint (week 6)

	N	Baseline		Endpoint		LSMean Change	LSMean Difference	P-value
		Mean	SD	Mean	SD			
Quetiapine 400 mg	54	96.9	16.41	72.5	20.35	-27.31	-8.16	0.043
Quetiapine 800 mg	55	98.4	15.73	70.3	17.28	-28.44	-9.29	0.009
Placebo	43	97.5	16.4	78	23.32	-19.15		

Modified from Sponsor Table 25 and 11.2.1.1.4 in Clinical Study Report

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Based on a request from the FDA, the Sponsor also performed a separate analysis excluding Dr. Gilliam's site (site #10) [see Section 3.2, Compliance with Good Clinical Practices].

Table 10. Primary Efficacy Variable (MMRM): PANSS Total Score Change from Baseline to Endpoint (Week 6) – Excluding Site #10

	LSMean Difference	P-value
Quetiapine 400 mg (N = 53)	-8.37	0.042
Quetiapine 800 mg (N = 54)	-9.15	0.012
Placebo (N = 43)		

From Sponsor Table 2 in Response Document – Gilliam site

Other Analyses

*Sensitivity Analysis*

The LOCF showed similar statistically significant results for both quetiapine groups as compared to placebo.

Table 11. Primary Efficacy Variable: PANSS Total Score Change from Baseline (LOCF)

Treatment Groups	N	LSMean Change	LSMean Difference	P-value(vs. placebo)
Quetiapine 400 mg	74	-25.76	-7.24	0.036
Quetiapine 800 mg	73	-27.23	-8.71	0.012
Placebo	73	-18.52		

Modified from Sponsor Table 11.2.1.2.3 in Clinical Study Report

*Analysis of Primary Endpoint over Time*

The following table summarizes the treatment effect over time based on the MMRM analysis.

Table 12. Change from randomization in the PANSS total score (MMRM) over time

Visit	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
	N	Mean	N	Mean	N	Mean	Diff	P-value*	Diff	P-value*
Day 07	72	-6.65	73	-8.23	72	-8.80	-1.58	0.410	-2.16	0.214
Day 14	72	-10.09	70	-14.24	71	-16.09	-4.15	0.098	-6.00	0.012
Day 21	65	-12.14	67	-20.37	68	-19.42	-8.23	0.006	-7.28	0.011
Day 28	57	-15.00	59	-22.72	65	-22.38	-7.72	0.023	-7.39	0.018
Day 35	51	-18.00	59	-24.68	62	-26.14	-6.68	0.085	-8.14	0.019
Day 42	43	-19.15	54	-27.31	55	-28.44	-8.16	0.043	-9.29	0.009

Note: extracted from Dr. Dinh's FDA statistical review; data from Sponsor's Study Report; Table 11.2.1.2.1  
 \* p-values not adjusted for multiplicity

*Secondary Efficacy Variables*

The CGI-S was statistically significant in favor of quetiapine 800 mg compared to placebo, but did not reach a statistically significant level for the quetiapine 400 mg group (Table 13). Both quetiapine treatment arms were statistically significantly different from placebo on the PANSS positive symptom subscale score at endpoint (Table 14). Neither quetiapine treatment arm demonstrated efficacy on the variable % responders at endpoint (Table 15).

Table 13. Secondary Efficacy Variable: CGI-S Change from Baseline to Endpoint (MMRM)

Treatment Groups	N	LSMean Change	LSMean Difference	P-value(vs. placebo)
Quetiapine 400 mg	55	-1.15	-0.34	0.1
Quetiapine 800 mg	55	-1.28	-0.47	0.018
Placebo	43	-0.081		

Modified from Sponsor Table 11.2.3.2.1.3 in Clinical Study Report

Table 14. Secondary Efficacy Variable: PANSS Positive Symptom Subscale Score Change from Baseline to Endpoint (MMRM)

Treatment Groups	N	LSMean Change	LSMean Difference	P-value(vs. placebo)
Quetiapine 400 mg	55	-8.56	-2.05	0.075
Quetiapine 800 mg	55	-9.34	-2.83	0.008
Placebo	43	-6.51		

From Sponsor Table 31 in Clinical Study Report (Study 112)

Table 15. Secondary Efficacy Variable: Percent of Responders ( $\geq 30\%$  reduction from baseline in PANSS total score at endpoint)

Treatment Groups	OC			LOCF		
	N	Responders N (%)	p-value	N	Responders N (%)	p-value
Quetiapine 400 mg	55	28 (51.9)	0.125	73	28 (38.4)	0.109
Quetiapine 800 mg	55	22 (40.0)	0.675	74	27 (36.5)	0.194
Placebo	43	17 (39.5)		73	19 (26.0)	

From Sponsor Table 27 in Clinical Study Report (Study 112)

## Conclusions

The efficacy of quetiapine in the acute treatment of schizophrenia in adolescents was demonstrated in this pivotal trial.

### 6.1.2 Subgroup Analyses

Our statistics team conducted exploratory subgroup analyses based on age ( $\leq 15$  yrs;  $> 15$  yrs), gender (M,F), race (Caucasian, others), and geographic regions (US vs. non-US). As noted in detail by Dr. Dinh in the FDA statistical review, the results trended in the same direction in favor of quetiapine in both the race or gender subgroups. Quetiapine appeared to show a significantly greater treatment effect in the  $\leq 15$  yrs age group. For the  $> 15$  yrs group, there seemed a larger placebo effect. Quetiapine appeared to show a greater improvement of treatment effect among the US patients than non-US patients.

### **6.1.3 Dose Response**

The treatment response was numerically greater in the 800 mg group (i.e., the placebo-subtracted LS mean difference of -8.16 in the 400 mg; -9.29 in the 800 mg quetiapine groups), but not statistically significantly different between the two doses.

### **6.1.4 Key Secondary Endpoints**

No key secondary endpoint was pre-specified in this study.

### **6.1.5 Effect Size**

The treatment effect size (change from baseline to endpoint in PANSS total scores around 8 to 9 points) observed in this study seems similar to the effect size observed in other schizophrenia trials.

### **6.1.6 Long-term Efficacy**

No adequate and well controlled data to address the question of long-term efficacy in this submission.

### **6.1.7 Pediatric Development**

This study was conducted in response to the Pediatric Written Request letter issued under pediatric exclusivity.

## **Efficacy Conclusions**

The sponsor has provided positive efficacy data for quetiapine in support of the claim for the acute treatment of schizophrenia in adolescents.

## **6.2 Studies Pertinent to Bipolar Mania Claim**

### **Rationale for Selection of Studies for Review**

Our efficacy review was focused on data collected in a single study D1448C00149 (Study 149), which was a 3-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of quetiapine fumarate (Seroquel) immediate-release tablets in daily doses of 400 mg and 600 mg compared with placebo in the treatment of children and adolescents (10 to 17 yrs of age) with bipolar mania.

## 6.2.1 Study 149

### Clinical Trial

Study 149 [Protocol D1441C00149] “A 3-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase IIIb study of the efficacy and safety of quetiapine fumarate (Seroquel) immediate-release tablets in daily doses of 400 mg and 600 mg compared with placebo in the treatment of children and adolescents with bipolar I mania”.

This study was conducted in 34 centers in the United States.

First patient enrolled 8/5/2004, last patient completed 7/10/2006.

### Methods/Study Design/Analysis Plan

This study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group 3-week trial in male and female inpatient and outpatient children and adolescents (age 10 – 17 years) with DSM-IV diagnosis of Bipolar I mania (confirmed by the K-SADS-PL). Following a medication washout period of 1 to 28 days, patients were randomized (1:1:1) to one of three treatment groups: quetiapine 400 mg/day, quetiapine 600 mg/day or placebo. Randomization was stratified by age (10 – 12 years, 13 – 17 years). Study medication was administered twice or three times daily per the judgment of the investigator. Quetiapine was titrated to the target fixed dose according to the following regimen:

Table 16. Quetiapine treatment regimens (mg/day) for administration

**Table 5 Quetiapine treatment regimens (mg/day) for administration twice daily**

Dose group	Time	Study day										
		1	2	3	4	5	6	7	8	9	10	11-21
400mg	AM	NA	50	100	100	200	200	200	200	200	200	200
	PM	50	50	100	200	200	200	200	200	200	200	200
600mg	AM	NA	50	100	100	200	200	300	300	300	300	300
	PM	50	50	100	200	200	300	300	300	300	300	300

AM Morning. NA Not Applicable. PM Evening.

According to this titration regimen, target fixed doses were reached by Day 5 (400 mg/day) and Day 7 (600 mg/day). Based on tolerability issues, investigators could administer study drug three times daily. No more than 400 mg was to be administered as a single dose.

For inclusion into the study, patients had to have a YMRS total score  $\geq 20$  at both screening and baseline. Patients with rapid cycling or who experienced a first manic episode were included. Patients could also have a secondary diagnosis of ADHD (see all inclusion/exclusion criteria in Appendix 9.5).

Allowable concomitant medications included benztropine for the treatment of emergent EPS, diphenhydramine (up to 50 mg/day) for “sleeplessness”, hydroxyzine (up to 100 mg/day not to exceed 4 days in any study week) for agitation or anxiety, lorazepam (up to 4 mg/day – not to exceed 4 days in any study week) orally or IM for the treatment of agitation or anxiety, propranolol for the treatment of akathisia. Ongoing treatment with select psychostimulants (methylphenidate, dextroamphetamine, mixed amphetamine salts, dexamethylphenidate) were allowed if the dose had been stable for  $\geq 30$  days before screening (no dose adjustments were allowed).

Discontinuation criteria were similar to Study 112.

Patients completing this study, or were discontinued due to worsening of their symptoms, or were discontinued due to an AE not related to quetiapine were given the option to enter a 26-week, open-label quetiapine study (D1441C00150).

*Efficacy assessments*

The primary efficacy assessment was the YMRS total score. Secondary efficacy assessments included the Clinical Global Impression-Bipolar Severity of Illness, Clinical Global Impression-Bipolar Global Improvement, Children's Global Assessment Scale, Children's Depression Rating Scale-Revised, Overt Aggression Scale-Modified and Caregiver Strain Questionnaire.

No secondary assessments were identified as key secondaries for purposes of inclusion in product labeling.

*Safety assessments*

Essentially the same as Study 112.

*Statistics*

The primary outcome variable was the change from baseline to Day 21 in the YMRS total score. The primary analysis was MMRM (unstructured covariance pattern). Baseline YMRS total score was used as a covariate, other variables in the model included age stratum, treatment, visit, and visit-by-treatment interaction. All statistical comparisons used 2-sided tests with a significance level of 0.050, unless otherwise specified. The two contrasts of interest were the 400 mg/day and the 600 mg/day quetiapine groups versus placebo and the Simes-Hommel step-up procedure was used for adjustment of the 2 primary comparisons.

An additional analysis using ANCOVA model with missing values imputed by the LOCF method was conducted to further assess robustness of the primary analysis.

Sample size determination: A total of 88 evaluable patients per treatment group (N = 264) would provide at least 85% power to detect a difference of 6 points between either the 400 mg/day or 600 mg/day quetiapine treatment group and the placebo group for the mean change from baseline in YMRS total score. A Bonferroni correction using an alpha = 0.025 for each dose comparison to placebo was used as a conservative approach for obtaining the sample size estimate. This sample size calculation assumed a standard deviation of 12 and a 2-tailed test at an overall experimental type I error rate of 0.05. An additional 66 (20%) patients were added to provide an estimate of 330 patients needed for screening. These additional patients were added to account for those patients who may be screened but who may not become evaluable.

No interim analyses were planned or performed.

Definitions of the ITT and safety populations were standard. ITT population: All randomized patients who were given study treatment and who had baseline and at least one post-baseline efficacy assessment for the YMRS.

Safety population: All randomized patients who were given study treatment.

## Results

### Demographics

The mean age (~13 years) was similar across the treatment groups and the distribution between children (10 – 12 years) and adolescents (13 – 17 years) was similar between groups. More males were enrolled in the quetiapine 600 mg/day and placebo groups. The majority of patients were Caucasian.

Table 17. Patient Demographics

	Quetiapine 400 mg/day N = 93	Quetiapine 600 mg/day N = 95	Placebo N = 89
Sex n (%)			
Male	47 (50.5)	55 (57.9)	54 (60.7)
Female	46 (49.5)	40 (42.1)	35 (39.3)
Age (years)			
Mean	13.1 (2.2)	13.2 (2.2)	13.3 (2.1)
Median	13	13	13
Range	10 - 17	9* - 17	10 - 17
Age distribution n (%)			
10 – 12 years	43 (46.2)	42 (44.2)	36 (40.4)
13 – 17 years	50 (53.8)	53 (55.8)	53 (59.6)
Race n(%)			
Caucasian	73 (78.5)	73 (76.8)	66 (74.2)
Black	12 (12.9)	14 (14.7)	12 (13.5)
Oriental	0	0	1 (1.1)
Other	8 (8.6)	8 (8.4)	10 (11.2)
Ethnic Group n (%)			
African-American	10 (10.8)	14 (14.7)	12 (13.5)
African-Caribbean	2 (2.2)	0	0
Hispanic	8 (8.6)	7 (7.4)	11 (12.4)
Native American	2 (2.2)	3 (3.2)	1 (1.1)
Not applicable	69 (74.2)	70 (73.7)	61 (68.5)
Other	2 (2.2)	1 (1.1)	2 (2.2)
Native Hawaiian/Pacific Islander	0	0	2 (2.2)

\*This patient was consented at 9 years old and was 10 years old by the start of study drug  
 From Sponsor Table 21 in Clinical Study Report

**Baseline Characteristics**

Select baseline characteristics are listed in Table 18. The treatment groups were well matched with regard to baseline characteristics of diagnosis and severity of illness. More patients in the quetiapine 400 mg/day group had comorbid ADHD. There was variability between the groups with regard to the number of manic/mixed episodes experienced in the past year.

Table 18. Baseline Characteristics

	Quetiapine 400 mg/day N = 93	Quetiapine 600 mg/day N = 95	Placebo N = 89
DSM-IV diagnosis n (%)			
Most recent episode manic	73 (78.5)	72 (75.8)	68 (76.4)
Most recent episode manic, severe, without psychotic features	14 (15.1)	14 (14.7)	14 (15.7)
Most recent episode manic, severe with psychotic features	5 (5.4)	5 (5.3)	7 (7.9)
Most recent episode mixed	0	1 (1.1)	0
Most recent episode mixed, severe without psychotic features	0	2 (2.1)	0
Most recent episode mixed, severe with psychotic features	1 (1.1)	1 (1.1)	0
Comorbid ADHD diagnosis n(%)	49 (52.7)	40 (42.1)	35 (39.3)
Baseline CGI-BP-Severity Score			
Mean (SD)	4.7 (0.75)	4.6 (0.71)	4.6 (0.64)
Range	3-7	3-7	4-7
Baseline YMRS score	29.4 (5.9)	29.6 (6.4)	30.7 (5.9)
Years since first known manic or mixed episode			
Mean (SD)	4.3 (3.1)	4.1 (3.0)	4.5 (2.9)
Total number of prior manic or mixed episodes over past year			
Mean (SD)	7.3 (38.7)	3.5 (11.2)	5.3 (21.9)
Years since first known depressed episode			
Mean (SD)	4.6 (3.0)	5.0 (2.8)	4.7 (2.5)
Total number of prior depressed episodes over past year			
Mean (SD)	1.1 (1.8)	3.7 (16)	2.4 (11.5)
Total number of bipolar hospitalizations over lifetime			
Mean (SD)	1.1 (1.8)	1.1 (2.5)	0.7 (1.5)
Years since last inpatient psychiatric hospitalization			
Mean (SD)	1.8 (1.5)	2.8 (2.5)	3.3 (3.3)
Has the subject been hospitalized for a suicide attempt?			
Yes n (%)	5 (5.4)	4 (4.2)	1 (1.1)
Current or prior exposure to quetiapine?			
Yes, n (%)	25 (26.9)	16 (16.8)	15 (16.9%)
Quetiapine average daily dose			
Mean (SD)	152 (124.1)	209 (187.1)	225 (203.1)

From Sponsor Table 22 in Clinical Study Report, baseline YMRS scores obtained from Table 11.2.1.2.3.

### Patient Disposition

A total of 393 patients were enrolled into the clinical trial. One hundred nine were screening failures, primarily due to not fulfilling eligibility criteria. A total of 284 patients were randomized.

Table 19. Patient Disposition

	Quetiapine 400 mg/day	Quetiapine 600 mg/day	Placebo
Randomized	95	98	91
Received Drug	95	98	90
<b>Discontinued Study</b>	19 (20.0%)	18 (18.4%)	25 (27.5%)
Adverse Event	15 (15.8%)	7 (7.1%)	4 (4.4%)
Met discontinuation criteria*	1 (1.1%)	2 (2.0%)	4 (4.4%)
Patient not willing to continue	1 (1.1%)	5 (5.1%)	5 (5.5%)
Lost to follow-up	0	1 (1.0%)	2 (2.2%)
Other**	2 (2.1%)	3 (3.1%)	10 (11.0%)
<b>Completed Study</b>	<b>76 (80%)</b>	<b>80 (81.6%)</b>	<b>66 (72.5%)</b>
Enrolled in OL study 150	73 (76.8%)	67 (68.4%)	68 (75.6%)

From Sponsor Figure 1 in Clinical Study Report

\*the majority of these discontinuations were due to lack of efficacy as defined by CGI-I scores per discontinuation criteria. [from Disposition of Each Subject document in submission].

\*\*examples of "other" discontinuations included noncompliance, family withdrew consent, moving out of state, lack of efficacy [from Disposition of Each Subject document in submission]

Table 20. Sample Sizes for ITT and Safety Populations

	Total	Quetiapine 400 mg/day	Quetiapine 600 mg/day	Placebo
ITT Population	277	93	95	89
Safety Population	283	95	98	90

### Concomitant Medications

Allowable concomitant medications included benztropine for the treatment of emergent EPS, diphenhydramine (up to 50 mg/day) for "sleeplessness", hydroxyzine (up to 100 mg/day not to exceed 4 days in any study week) for agitation or anxiety, lorazepam (up to 4 mg/day – not to exceed 4 days in any study week) orally or IM for the treatment of agitation or anxiety, propranolol for the treatment of akathisia. Ongoing treatment with select psychostimulants (methylphenidate, dextroamphetamine, mixed amphetamine salts, dexmethylphenidate) were allowed if the dose had been stable for  $\geq 30$  days before screening (no dose adjustments were allowed).

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The use of psychostimulants was 19.4% in the quetiapine 400 mg/day group, 11.6% in the quetiapine 600 mg/day group and 11.2% in the placebo group. The use of psychostimulants was less than the overall diagnosis of comorbid ADHD in each treatment group (~40-50%), with the quetiapine 400 mg/day group having a higher proportion of patients with comorbid ADHD than the other two treatment groups (see Table 18). Not unexpectedly, the use of antihistamines and lorazepam was higher in the placebo group.

Table 21. Concomitant Medication Use

	Quetiapine 400 mg/day N = 93	Quetiapine 600 mg/day N = 95	Placebo N = 89
Antidepressants			
Sertraline	1 (1.1%)	0	0
Mood Stabilizers			
Valproate	0	0	1 (1.1%)
Lithium	1 (1.1%)	0	0
Psychostimulants			
Atomoxetine	1 (1.1%)	0	0
Dexamphetamine	6 (6.5%)	2 (2.1%)	3 (3.4%)
Methylphenidate	11 (11.8%)	9 (9.5%)	7 (7.9%)
Antihistamines*			
Diphenhydramine	5 (5.4%)	4 (4.2%)	9 (10.1%)
Hydroxyzine	4 (4.3%)	1 (1.1%)	4 (4.5%)
Benzodiazepines			
Lorazepam	8 (8.6%)	5 (5.3%)	10 (11.2%)

From Sponsor table 11.1.7.5 in Clinical Study Report

\*Used for sedation or treatment of agitation

### *Important Protocol Violations*

As with Study 112, the majority of major protocol violations were patients using anxiolytics/hypnotics not specifically permitted or other concomitant medication violations. Concomitant medication use is discussed in the previous section. No other major protocol violations were noted that would impact the overall interpretation of the study results.

Of note, though major protocol violations were included in subject discontinuation criteria in the protocol, it does not appear that any patients were discontinued from the study based on this criterion.

### *Dosing*

The study used two fixed doses of quetiapine, 400 mg/day and 600 mg/day, vs. placebo.

### Efficacy Findings

#### Primary Efficacy Analysis

The MMRM analysis showed both quetiapine 400 mg/day and quetiapine 600 mg/day were statistically significantly superior to placebo.

Table 22. Primary Efficacy Variable (MMRM): YMRS Total Score Change from Baseline to Endpoint (week 6) in the MITT Patient Population

	N	Baseline		Mean change from baseline to endpoint		LSMean Change	LSMean Difference	P-value vs. placebo
		Mean	SD	Mean	SD			
Quetiapine 400 mg	76	29.2	5.9	-15.3	8.45	-14.25	-5.21	<0.001
Quetiapine 600 mg	81	29.2	5.96	-15.8	9.32	-15.06	-6.56	<0.001
Placebo	67	30	5.45	-10.1	10.28	-9.04		

Modified from Sponsor Table 24 and 11.2.1.2.1 in Clinical Study Report

Based on a request from the FDA, the Sponsor also performed a separate analysis excluding Dr. Gilliam's site (site #10) [see Section 3.2, Compliance with Good Clinical Practices].

Table 23. Primary Efficacy Variable (MMRM): YMRS Total Score Change from Baseline to Endpoint (Week 3) – Excluding Site #10

	LSMean Difference	P-value
Quetiapine 400 mg (N = 67)	-5.56	< 0.001
Quetiapine 600 mg (N = 73)	-6.92	< 0.001
Placebo (N = 59)		

From Sponsor Table 2 in Response Document – Gilliam site

#### Sensitivity Analysis

The primary analysis model was repeated using the per-protocol population. This analysis corroborated with the primary analysis as noted by Dr. Dinh in his statistical review (table 14).

In addition, an ANOVA model with missing data imputed by the LOCF method in the MITT population showed similar statistically significant results for both quetiapine groups as compared to placebo.

Table 24. Primary Efficacy Variable: YMRS Total Score Change from Baseline (LOCF)

Treatment Groups	N	LSMean Change	LSMean Difference	P-value(vs. placebo)
Quetiapine 400 mg	93	-13.42	-5.15	<0.001
Quetiapine 600 mg	95	-15.18	-6.9	<0.001
Placebo	89	-8.28		

Modified from Sponsor Table 11.2.1.2.3 in Clinical Study Report

*Analysis of Primary Endpoint over Time*

The following table summarizes the treatment effect over time based on the MMRM analysis.

Table 25. Change from Randomization in the YMRS total score (MMRM) Over Time

Visit	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
	N	Mean	N	Mean	N	Mean	Diff	P-value*	Diff	P-value*
Day 04	64	-5.01	81	-8.05	75	-6.84	-3.05	0.015	-1.83	0.120
Day 07	84	-6.78	88	-11.88	90	-11.83	-5.10	<0.001	-5.05	<0.001
Day 14	73	-8.47	79	-13.26	82	-14.76	-4.79	0.001	-6.29	<0.001
Day 21	67	-9.04	76	-14.25	81	-15.60	-5.21	<0.001	-6.56	<0.001

Note: extracted from Dr. Dinh's FDA statistical review, table 16; data from Sponsor's Study Report; Table 11.2.1.2.1  
 \* p-values not adjusted for multiplicity

*Secondary Efficacy Variables*

The sponsor claims that improvement of manic symptoms in this patient population treated by quetiapine, as assessed by the YMRS total score change from baseline at Day 4 and Day 7 for 400 mg quetiapine, and Day 7 for 600 mg quetiapine (see table above).

The sponsor also claims that quetiapine 400 mg and 600 mg were superior to placebo in improving a broad range of mania symptoms in this patient population assessed by CGI-BP severity of illness at Day 7 and 21, GCI-BP Global Improvement (Overall Bipolar Illness) scale at Day 21, percentage of patients with remission (defined as a YMRS-total score <12 at Day 21), and percentage of patients with response (defined as a >50% reduction from baseline in the YMRS total score) at Day 7 and 21. None of these secondary variables were pre-specified as a key secondary variable. For details, refer to Sponsor's Appendix Tables in section 11.2 of the NDA submission regarding supporting data for these secondary variables

Table 26. Secondary Efficacy Variable: Percent of Responders ( $\geq 50\%$  reduction from baseline in YMRS total score at endpoint)

Treatment Groups	OC			LOCF		
	N	Responders N (%)	p-value	N	Responders N (%)	p-value
Quetiapine 400 mg	76	49 (64%)	0.001	93	51 (55%)	< 0.001
Quetiapine 600 mg	81	47 (58%)	0.005	95	53 (56%)	< 0.001
Placebo	67	25 (37%)		89	25 (28%)	

From Sponsor Tables 26 and 11.2.1.6.2 in Clinical Study Report (Study 149)

Table 27. Secondary Efficacy Variable: Percent of Remitters ( $\leq 12$  on YMRS total score at endpoint)

Treatment Groups	OC			LOCF		
	N	Remitters N (%)	p-value	N	Remitters N (%)	p-value
Quetiapine 400 mg	76	40 (53%)	0.010	93	42 (45%)	0.003
Quetiapine 600 mg	81	44 (54%)	0.003	95	49 (52%)	< 0.001
Placebo	67	20 (30%)		89	20 (22%)	

From Sponsor Tables 27 and 11.2.1.8.2 in Clinical Study Report (Study 149)

**Conclusions**

The efficacy of quetiapine in the acute treatment of bipolar mania in children and adolescents (ages 10 to 17 yrs) was demonstrated in this pivotal trial.

## 6.2.2 Subgroup Analyses

Our statistics team conducted exploratory subgroup analyses based on age (10-12 yrs; 13-17 yrs), gender (M,F), and race (Caucasian, others). As noted in detail by Dr. Dinh in the FDA statistical review (tables 26, 27 and 28), the results trended in the same direction in favor of quetiapine in all these subgroup analyses.

Table 28. Study D1448C00149: Sponsor's primary efficacy results by age: change from baseline to week 3 in the YMRS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
<i>Age 10-12</i>			
Sample size at Week 3	26	32	37
LS Means	-8.68	-13.49	-17.06
Difference from placebo (95% confidence interval)		-4.81 (-9.73, 0.12)	-8.38 (-13.05, -3.71)
<i>Age 13 - 17</i>			
Sample size at Week 3	41	44	44
LS Means	-9.35	-14.92	-14.39
Difference from placebo (95% confidence interval)		-5.57 (-9.18, -1.96)	-5.04 (-8.83, -1.24)

From Statistician's review, Table 28

Inclusion criteria indicated that patients with rapid-cycling bipolar disorder could be enrolled into the study. The Sponsor did not indicate whether any patients with rapid-cycling disorder were enrolled nor, if enrolled, if there was any differential efficacy based on a subgroup analysis. The Sponsor has been asked to provide this information to the Division.

## 6.2.3 Dose Response

The treatment response was numerically greater in the higher dose 600 mg quetiapine group (i.e., the placebo-subtracted LS mean difference of -5.2 in the 400 mg; -6.6 in the 600 mg quetiapine group), though not statistically significantly different.

## 6.2.4 Key Secondary Endpoints

No key secondary endpoint was pre-specified in this study.

## 6.2.5 Effect Size

The treatment effect size (change from baseline to endpoint in YMRS total scores around 5 points) observed in this study seems similar to the effect size observed in other mania trials.

## 6.2.6 Long-term Efficacy

No adequate and well controlled data to address the question of long-term efficacy in this submission.

## 6.2.7 Pediatric Development

This study was conducted in response to the Pediatric Written Request letter issued on 2/11/2003 under pediatric exclusivity.

## Efficacy Conclusions

The sponsor has provided positive efficacy data for quetiapine in support of the claim for the acute treatment of bipolar mania in children adolescents.

# 7 Review of Safety

## Safety Summary

*Note: a comprehensive review of the effects of quetiapine on weight, BMI, glucose and lipids in children/adolescents is ongoing (per the Division's separate request for these data in January 2008). This review will also include dose-related effects of quetiapine on these metabolic parameters (per the Division's additional request in February 2009).*

*Several additional requests for information regarding specific safety signals have been submitted to the Sponsor. When all of these data have been reviewed, the Sponsor's proposed product labeling will also be reviewed in a separate addendum to this clinical review.*

No deaths occurred in the clinical trials included in this submission. Similar percentages of patients had serious adverse events in the quetiapine and placebo groups [Study 112: 6.1% in the quetiapine groups combined vs. 5.3% in the placebo group; Study 149: 4.7% in the quetiapine groups combined vs. 3.3% in the placebo group]. The majority of serious adverse events were potentially related to the underlying psychiatric diagnosis. Similarly, many of the discontinuations due to adverse events included events that were potentially related to the underlying psychiatric diagnoses, however, the majority of discontinuations due to adverse events included somnolence, sedation, lethargy and fatigue.

In both Studies 112 and 149, the common adverse events were similar to that already established for quetiapine in the adult clinical trials programs. Sedation/somnolence was the most common adverse event [Study 112: 33% quetiapine 400 mg/day, 35% quetiapine 800 mg/day, 11% placebo; Study 149: 49% quetiapine 400 mg/day, 57% quetiapine 600 mg/day, 14% placebo]. In both studies, tachycardia occurred in ~5% of patient in the quetiapine 400 mg/day groups, ~8% in the quetiapine 600 – 800 mg/day groups and 0 patients in the placebo groups.

In Study 112, the rates of EPS were greater in the quetiapine groups compared to placebo (12.3% in the quetiapine 400 mg/day group, 13.5% in the quetiapine 800 mg/day group and 5.3% in the placebo group). Rates of EPS were lower in Study 149, but were greater in the quetiapine groups compared to placebo (4.2% in the quetiapine 400 mg/day group, 3.1% in the quetiapine 600 mg/day group and 1.1% in the placebo group).

The clinical chemistry findings for Studies 112 and 149 were similar to that already established for quetiapine in the adult clinical trials programs. Mean increases in quetiapine groups occurred for AST, ALT, alkaline phosphatase, total cholesterol, LDL and triglycerides. A mean decrease in glucose was noted in Study 112 while Study 149 showed a mean increase in the quetiapine groups (+3.5 mg/dL for quetiapine 400 mg/day, +3.7 mg/dL for quetiapine 600 mg/day vs. -1.2 mg/dL for placebo). Mean change in TSH concentrations were variable within and between studies while the overall effect on free T4 and total T4 was a mean decrease. Mean prolactin concentrations decreased in Study 112 and increased in Study 149 (+2.8 for quetiapine 400 mg/day, +1.9 for quetiapine 600 mg/day vs. -1.1 for placebo). The findings for hematology included the known effect of decreases in neutrophils in the quetiapine groups [Study 112: -0.07  $10^9/L$  for quetiapine 400 mg/day, -0.12  $10^9/L$  quetiapine

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800 mg/day vs. +0.36 10<sup>9</sup>/L for placebo group], decrements occurred in all treatment groups (including placebo) in Study 149.

A new signal that emerged in the children/adolescent population that was not present in the adult clinical trials programs was a significant increase in pulse, systolic blood pressure and diastolic blood pressure.

Vital Signs: Mean Change from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day	Quetiapine 800 mg/day	Placebo
Supine pulse (bpm)	6	3.9	-1.4
Supine Systolic BP (mmHg)	2	1	-1.6
Supine Diastolic BP (mmHg)	1.3	0.2	0.1
Standing Pulse (bpm)	6.3	2.2	-2.5
Standing Systolic BP (mmHg)	2.3	-0.4	-1.7
Standing Diastolic BP (mmHg)	2.1	1.1	-1.2

Vital Signs: Mean (SD) Change from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg/day	Quetiapine 600 mg/day	Placebo
Supine pulse (bpm)	8.8	10.6	-0.8
Supine Systolic BP (mmHg)	0.4	2.4	-2.7
Supine Diastolic BP (mmHg)	1.3	3.1	1.0
Standing Pulse (bpm)	9.6	11.3	0.1
Standing Systolic BP (mmHg)	1.0	1.3	-0.8
Standing Diastolic BP (mmHg)	1.	1.7	0.2

Clinically important shifts in vital signs at any time also indicated higher percentages of patients with increases in supine pulse, systolic and diastolic blood pressures in the quetiapine groups compared to placebo (Sponsor has been asked to provide these data for standing vital signs). When comparing the clinically important shifts to high in vital signs between patients 10 - 12 years of age and patients 13 to 17 years of age, a greater percentage of patients experienced these shifts for most categories in the 10 - 12 years cohort (see review).

Clinically Important Shifts (Select) in Vital Signs At Any Time (Studies 112 and 149 Pooled)

	Shift	Quetiapine N = 340	Placebo N = 165
Supine Pulse (bpm)	> 120	8.1%	0
	≥ 15 increase	50.7%	18.4%
Supine Systolic BP (mmHg)	> 121*	14.2	5.9%
	≥ 20 increase	15.2	5.5%
Supine Diastolic BP (mmHg)	≥ 78*	16.8%	7.3%
	≥ 10 increase	40.6%	24.5%
	≥ 30 increase	1.5%	1.8%

\*Definitions used for cut-offs differed by gender and age, see review

In Study 112 (6-week study), mean increases in weight occurred in the quetiapine groups (+1.9 kg in 400 mg, +1.5 kg in 800 mg) compared to a mean decrease (-0.1 kg) in the placebo group. In Study 112, 23.2% of patients in the quetiapine 400 mg/day group, 18.2% of patients in the quetiapine 800 mg/day group and 6.8% of patients in the placebo group had a ≥ 7% weight gain.

In Study 149 (3-week study) mean increases in weight also occurred in the quetiapine groups (+1.7 kg in 400 mg, +1.7 kg in 600 mg) compared to a mean increase of 0.4 kg in the placebo group. In Study 149, 14.5% of patients in the quetiapine 400 mg/day group, 9.9% of patients in the quetiapine 600 mg/day group and 0% patients in the placebo group had a  $\geq 7\%$  weight gain. In a pooled analysis (Studies 112 and 149), the percent of patients who gained  $\geq 7\%$  weight was 14.1% for quetiapine-treated patients 10 to 12 years old (compared to 0% in the placebo groups) and 18% for quetiapine-treated patients 13 to 17 years old (compared to 3.1% in the placebo groups). In the 26-week open label study, similar percentages of patients in the quetiapine groups and placebo groups had shifts of  $\geq 0.5$  BMI z-score from baseline at anytime, end of treatment and final visit.

Other than effects on heart rate, which were consistent with vital signs data, there were no significant findings with regard to ECG data. Study 150, the open-label 26-week extension study, obtained slit-lamp examinations at baseline and end of study. Three patients (< 1%) had a shift from normal to abnormal – the Sponsor has been asked to provide more clinical information on these abnormal readings.

A suicidality assessment (similar to the Columbia-type assessment) was included in these clinical trials. Five (1.5%) patients in the pooled analysis of Studies 112 and 149 had suicidal behavior/ideation compared to 0 in the placebo groups. The calculated relative risk for quetiapine compared to placebo did not reach statistical significance.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The trials primarily reviewed for safety data include the two pivotal acute trials, Study 112 (schizophrenia) and Study 149 (bipolar I mania) and the 26-week open-label extension to these two acute trials, Study 150. Study 028, a small open-label pharmacokinetic study, was reviewed for occurrences of serious adverse events and discontinuations due to adverse events. No events in these categories occurred in Study 028.

The safety population for Study 112 included 73 patients in the quetiapine 400 mg/day group, 74 patients in the quetiapine 800 mg/day group and 90 patients in the placebo group.

The safety population for Study 149 included 95 patients in the quetiapine 400 mg/day group, 98 patients in the quetiapine 600 mg/day group and 75 patients in the placebo group.

The safety population for Study 150 included 381 patients treated with open-label quetiapine [mean daily dose 599 (256.8) mg over a median of 181 days on study medication].

Three hundred eighty one patients were enrolled into Study 150, 237 (62.2%) completed the study. Disposition of patients is in Table 29. Approximately 75% of patients in studies 112 and 149 entered the open-label extension Study 150. Since the dose and drug assignments from the acute studies were not known, all patients began treatment with quetiapine on Day 1 with a dose of 50 mg followed by dose escalation to 400 mg by Day 5. On Day 5 and thereafter, the target dose of 400 mg was maintained or increased, by no more than 100 mg/day, up to 800 mg according to clinical response and investigator discretion. Dose could be reduced to 200 mg/day based on tolerability.

Table 29. Patient Disposition (Study 150)

	Quetiapine Open-Label
<b>Enrolled</b>	<b>381</b>
<b>Discontinued Study</b>	144 (37.8%)
Adverse Event	40 (10.5%)
Met discontinuation criteria	13 (3.4%)
Patient not willing to continue	42 (11%)
Lost to follow-up	33 (8.7%)
Other**	16 (4.2%)
<b>Completed Study</b>	<b>237 (62.2%)</b>

From Sponsor Figure 1 in Clinical Study report for Study 150

### 7.1.2 Categorization of Adverse Events

An audit of adverse event categorization and the use of MedDRA preferred terms was performed by reviewing a small sample of case report forms and comparing them to the corresponding narrative summary and the MedDRA line listing. No major deficiencies were found.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Sponsor provided some pooled safety analyses for the two pivotal trials that were provided in a clinical summary of safety document. These two pivotal trials differed in doses used (400 and 800 mg/day quetiapine in Study 112 and 400 and 600 mg/day quetiapine in Study 149) and study duration (6 weeks in Study 112 and 3 weeks in Study 149); and most of the safety data were provided separately in the respective clinical study reports.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The mean daily dose and mean duration of exposure for patients treated with quetiapine are provided in Table 30. Though these were fixed dose trials, the mean daily dose is lower than the target fixed dose due to the titration period.

Table 30. Mean Daily Dose and Mean Duration of Exposure (Studies 112, 149 and 150)

	Quetiapine 400	Quetiapine 800
Study 112	Quetiapine 400	Quetiapine 800
N	73	74
Mean daily dose (mg/day)	308 (56)	568 (130)
Mean duration of exposure (days)	40	40
Study 149	Quetiapine 400 mg	Quetiapine 600
N	95	98
Mean daily dose (mg/day)	287 (81)	404 (115)
Mean duration of exposure (days)	21	20
Study 150	Quetiapine	
N	380	
Mean daily dose (mg/day)	599	
Mean duration of exposure (days)	146	

From Summary of Clinical Safety and Clinical Study Report documents (112, 149 and 150)

The Sponsor did not provide summary data for patient years of exposure or an exposure by subject age cohort.

In the pooled analysis for Studies 112 and 149, most patients remained on the BID dosing schedule and 18.8% were switched to a TID dosing schedule based on tolerability issues as per the clinical judgment of the investigator.

### 7.2.2 Explorations for Dose Response

Dose response relationships could be explored in each of the two individual pivotal studies as they employed fixed-dose study designs. In general, the higher doses were associated with some additional numerical improvement in efficacy rating scale scores compared to the lower doses, but not statistically significantly different.

### 7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

### 7.2.4 Routine Clinical Testing

Given the known adverse event profile in the adult clinical trials programs, the type and frequency of vital sign, clinical laboratory, and ECG parameters measured and reported seems adequate. The schedule of safety assessments for Studies 112, 149 and 150 are in Appendices 9.4, 9.6 and 9.10.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

No new issues were identified.

### **7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

Atypical antipsychotics have been associated with several safety issues. Among the major safety issues are increased mortality in elderly patients with dementia-related psychosis, suicidality in children and adolescents, clinical worsening and suicidality, neuroleptic malignant syndrome, tardive dyskinesia (TD), orthostatic hypotension, hyperglycemia and diabetes mellitus.

The sponsors of atypical antipsychotics have been asked to provide additional data and pooled analyses for the metabolic profile safety signals. This includes AstraZeneca who have been asked to provide data and analyses for quetiapine IR and quetiapine XR for effects on lipids (cholesterol, HDL, LDL, triglycerides), glucose (glucose, HbA1c, UA glucose), and weight for both adults and pediatric subjects (see Division letter January 8, 2008). The Sponsor recently provided these data on 6/26/08 with an analysis of dose-related effects on metabolic parameters provided in February 2009 by Division request. The adult metabolic data review was completed in 03/2009; and was part of the discussion at the PDAC meeting on 4/8/2009. The pediatric metabolic data are currently under review.

## **7.3 Major Safety Results**

### **7.3.1 Deaths**

No deaths occurred in acute studies 112 or 149 or the open-label extension study 150.

### **7.3.2 Nonfatal Serious Adverse Events**

Most of the serious adverse events were potentially related to the underlying psychiatric disorder (e.g. schizophrenia, psychotic disorder, irritability, aggression, delusion, bipolar disorder, mania). Two patients experienced syncope (one in Study 149, one in Study 150), one patient experienced a serious drug rash (Study 149), one patient experienced neutropenia (Study 150) and one patient experienced hypertensive crisis (Study 150). Some comments regarding these cases appear after the tables of serious adverse events.

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Table 31. Serious Adverse Events – Study 112

	Patient	Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)	Action taken with Study Drug
Quetiapine 400	(b) (6)	M, 15	Schizophrenia	3	Moderate	17	None
		M, 17	Hallucination (visual)	26	Severe	13	None
		F, 16	Hypersensitivity*	35	Mild	7	Temporarily stopped
		F, 14	Psychotic disorder	30	Severe	4	Stopped
Quetiapine 800	(b) (6)	M, 14	Schizophrenia	26	Moderate	6	None
		M, 14	Aggression	2	Severe	11	None
		F, 17	Agitation	12	Severe	10	None
			Restlessness	12	Severe	10	None
			Verbal Abuse	12	Severe	13	None
			Irritability	12	Severe	20	None
		F, 15	Wound abscess*	23	Moderate	16	None
		M, 17	Amoebiasis	7	Mild	7	Temporarily stopped
Placebo	(b) (6)	M, 16	Delusion	5	Severe	8	Stopped
		M, 15	Schizophrenia	14	Severe	6	None
		F, 15	Aggression	19	Moderate	6	None
			Insomnia	24	Moderate	24	None
		M, 14	Pharyngotonsillitis	19	Moderate	11	None

From Sponsor Table 46 in Clinical Study Report

\*Investigator terms: Hypersensitivity: hypersensitivity reaction probably secondary to food, Wound abscess: infected wound/abscess formation on plantar aspect of right foot

Table 32. Serious Adverse Events – Study 149

	Patient	Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)	Action taken with Study Drug
Quetiapine 400 mg	(b) (6)	F, 15	Bipolar disorder	8	Severe	13	No
		M, 12	Bipolar disorder	8	Severe	7	Stopped
			Suicidal ideation	8	Severe	7	Stopped
		F, 12	Bipolar disorder	6	Moderate	Unknown	Stopped
		M, 15	Aggression	2	Severe	5	Stopped
			Mania	2	Severe	5	Stopped
		M, 12	Syncope	8	Moderate	1	Stopped
Quetiapine 600 mg	(b) (6)	M, 14	Staphylococcal infection	16	Severe	Unknown	None
		F, 9	Drug rash with eosinophilia and systemic symptoms	11	Mild	12	Stopped
		M, 15	Aggression	25	Moderate	8	None
		F, 15	Bipolar disorder	21	Severe	12	Stopped
Placebo	(b) (6)	M, 13	Bipolar disorder	3	Severe	20	None
		M, 17	Bipolar disorder	10	Severe	4	Stopped
		M, 14	Bipolar disorder	14	Severe	2	None

From Sponsor Table 48 in Clinical Study Report

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Table 33. Serious Adverse Events – Study 150 (open-label quetiapine)

Prior DB Trial/Treatment	Patient	Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)	Action taken with Study Drug	
112/PC	(b) (6)	M, 13	Abnormal behavior	61	Severe	8	Stopped	
149/PC		M, 14	Schizophrenia	61	Severe	8	Stopped	
149/PC		M, 13	Aggression	35	Severe	4	Temporarily stopped	
149/PC		M, 13	Bipolar disorder	31	Severe	3	None	
149/PC		M, 13	Bipolar disorder	48	Severe	9	None	
112/PC		F, 15	Constipation	128	Severe	3	None	
149/PC		F, 13	Bipolar disorder	167	Moderate	15	None	
149/PC		F, 12	Bipolar disorder	151	Severe	9	Stopped	
112/PC		F, 16	Physical assault	90	Severe	19	Stopped	
149/PC		M, 16	Mania	192	Moderate	8	None	
149/PC		F, 16	Syncope	34	Severe	1	Stopped	
112/PC		F, 17	Schizophrenia	19	Severe	2	Temporarily stopped	
112/PC		M, 18	Delusion	115	Severe	16	None	
				Hostility	115	Severe	16	
				Irritability	115	Severe	16	
112/PC		M, 17	Urinary Tract Infection	13	Mild	10	None	
112/PC		M, 15	Upper Respiratory Tract Infection	38	Severe	5	None	
149/Q 400		M, 10	Disinhibition	20	Severe	15	None	
149/Q 400		M, 12	Bipolar disorder	127	Severe	8	Dose Change	
112/Q 400	F, 17	Schizophrenia	56	Severe	7	Dose Change		
		Schizophrenia	90	Severe	22	None		
112/Q 400	F, 17	Schizophrenia	158	Severe	12	None		
		Hyperglycemia	213	Severe	8	None		
		Schizophrenia	213	Severe	51	None		
149/Q 400	M, 15	Overdose	19	Severe	8	Temporarily stopped		
149/Q 400	M, 15	Bipolar disorder	101	Severe	20	None		
149/Q 400	F, 15	Bipolar disorder	22	Severe	21	None		
112/Q 400	M, 15	Paroxysmal perceptual alteration	74	Severe	10	Stopped		
		Bacterial infection	108	Severe	Unknown	None		
112/Q 400	M, 17	Schizophrenia	29	Severe	9	None		
149/Q 400	F, 12	Bipolar disorder	3	Moderate	11	None		
149/Q 400	F, 13	Appendicitis	3	Severe	2	Temporarily stopped		
149/Q 400	F, 12	Bipolar disorder	46	Moderate	3	Stopped		
112/Q 400	M, 14	Hypertensive crises	129	Severe	1	None		
		Schizophrenia	129	Mild	84	None		
112/Q 400	F, 15	Suicide attempt	159	Severe	5	Stopped		
		Psychotic disorder	159	Severe	36	Stopped		
112/Q 400	M, 17	Schizophrenia	9	Severe	34	None		
112/Q 400	F, 14	Pulmonary hypertension	84	Mild	40	Stopped		
112/Q 400	M, 17	Aggression	43	Severe	7	None		
		Aggression	78	Moderate	9	None		
149/Q 600	M, 12	Bipolar disorder	98	Severe	7	Stopped		
112/Q 800	M, 16	Schizophrenia	204	Severe	9	None		
149/Q 600	M, 15	Bipolar disorder	5	Moderate	6	None		
		Cellulitis Staph	161	Moderate	13	None		
		Bipolar disorder	202	Severe	10	None		
149/Q 600	F, 16	Bipolar disorder	5	Severe	13	None		
149/Q 600	M, 14	Overdose	181	Severe	1	Stopped		
149/Q 600	M, 11	Appendicitis	66	Severe	4	Temporarily stopped		
149/Q 600	M, 10	Neutropenia	28	Severe	29	Stopped		
112/Q 800	M, 14	Schizophrenia	162	Severe	Unknown	Stopped		
		Schizophrenia	183	Severe	12	Stopped		
112/Q 800	M, 17	Psychotic disorder	84	Severe	Unknown	None		
112/Q 800	M, 16	Aggression	59	Severe	29	None		
112/Q 800	M, 15	Decreased appetite	28	Severe	4	None		
		Hallucination, auditory	29	Severe	Unknown	None		
112/Q 800	F, 16	Pyrexia	14	Mild	7	None		

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112/Q 800	(b) (6)	M, 17	Typhoid fever	27	Mild	7	None
			Agitation	6	Moderate	13	None
			Restlessness	6	Moderate	13	None
			Amoebiasis	66	Moderate	10	Dose changed
112/Q 800		F, 17	Drug toxicity (benzo)	52	Mild	4	Temporarily stopped
112/Q 800		M, 17	Myocarditis post infection	98	Mild	30	Dose changed

From Sponsor Table 11.3.4.2 in Study 150 Clinical Study Report

Comments from narratives:

*Hypersensitivity* (b) (6), Study 112) – patient experienced sudden appearance of maculopapular rash over upper and lower extremities and the cervical area, afebrile. Study medication was stopped. Patient recovered with treatment (hydroxyzine, prednisone). No comments regarding food allergies.

*Syncope* (b) (6), Study 149) – patient walking to school when stopped by a security guard for suspicion of substance abuse. Patient was asked to perform a maneuver involving tilting his head back and placing his index finger to his nose. During the procedure, he fainted and remained unconscious for approximately 10 minutes. He was lethargic and sleepy for several hours after the event (no chest pain, no SOB, no seizure activity reported). Event resolved on the same day without hospitalization.

*Drug rash* (b) (6), Study 149) – On day 11, rash of small papules on face and torso, no fever. Day 13, presented to ER with erythematous, blanching, pruritic rash on the face, arms, palms of both hands, abdomen, back, buttocks, legs and feet. During ER stay temperature increased to 102.3 degrees F with swelling of eyes and face. Narrative noted that eosinophils were high, but value not available. Study medication was stopped on Day 13. Patient was treated (oral and IV diphenhydramine, oral hydroxyzine prn, and topical steroid cream) and discharged on Day 22. Impression was allergy to quetiapine.

*Hypertensive crises* (b) (6) Study 150) - BP 150/95, resolved same day, narrative does not indicate that treatment was administered. There was no interruption or change in quetiapine dose. More information has been requested from the Sponsor.

*Suicide attempt* (b) (6), Study 150)– more information has been requested from Sponsor. Of note, the patient also experienced neutropenia with an ANC of 0.46 on Day 85. The next WBCs were performed on days 89 and 96 but without a differential. The next available ANC was on Day 169, the event had resolved with ANC = 2.82.

*Neutropenia* (b) (6), Study 150) – Day 28 ANC =  $1.40 \times 10^9/L$ . Dose of study medication reduced, ANC continued to fall reaching  $1.22 \times 10^9/L$  on Day 49, patient was discontinued. Recovery on Day 56 with ANC =  $2.33 \times 10^9/L$ .

### 7.3.3 Dropouts and/or Discontinuations

Many of the discontinuations due to adverse events were potentially related to the underlying psychiatric disorder (e.g. schizophrenia, delusion, bipolar disorder). The majority of the other adverse events leading to discontinuation were somnolence, sedation, lethargy and fatigue. There were also a number of discontinuations due to syncope and orthostatic hypotension.

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Table 34. Discontinuations due to Adverse Events – Study 112

	Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)
Quetiapine 400	M, 15	Somnolence	2	Moderate	26
	M, 14	Neutropenia	42	Mild	Unk
	F, 13	Schizophrenia	15	Severe	8
	F, 15	Anxiety	1	Moderate	Unk
	M, 17	Elevated Mood	10	Moderate	Unk
Quetiapine 800	M, 17	Somnolence	2	Moderate	3
	M, 13	Dysarthria	10	Severe	3
		Fatigue	10	Severe	3
	F, 14	Rubella	44	Mild	15
	F, 13	Depression	16	Severe	Unk
		Suicidal ideation	27	Mild	Unk
	F, 15	Dyspnoea	15	Moderate	Unk
	M, 16	Nausea	9	Moderate	8
		Somnolence	9	Moderate	8
	M, 15	Sedation	2	Moderate	Unk
Placebo	M, 16**	Delusion	5	Severe	8
	F, 16	Schizophrenia	22	Moderate	Unk

From Sponsor Table 48 in Clinical Study Report

\*\*Same patient as listed in Table 31

Table 35. Discontinuations due to Adverse Events – Study 149

	Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)
Quetiapine 400	M, 17	Fatigue	7	Mild	23
	F, 17	Somnolence	1	Mild	Unknown
	M, 12**	Bipolar disorder	8	Severe	7
		Suicidal ideation	8	Severe	7
	F, 10	Sedation	2	Moderate	Unknown
	M, 12	Irritability	11	Moderate	Unknown
		Hostility	13	Severe	Unknown
	F, 13	Sedation	1	Severe	3
	F, 12	Syncope	5	Moderate	1
	F, 12**	Bipolar disorder	6	Moderate	Unknown
	F, 16	Bradyphrenia*	2	Moderate	3
		Clumsiness	2	Mild	3
		Irritability	2	Moderate	3
		Sedation	2	Moderate	9
	M, 15**	Aggression	2	Severe	5
		Mania	2	Severe	5
	F, 12	Somnolence	2	Mild	Unknown
	M, 13	Sedation	1	Mild	6
	M, 13	Sedation	2	Severe	2
	M, 12**	Tympanic membrane perforation	8	Moderate	Unknown
		Syncope	8	Moderate	1
	F, 17	Fatigue	1	Severe	Unknown
		Hypotension	1	Moderate	Unknown
	Somnolence	1	Severe	Unknown	
Quetiapine 600 mg	F, 15	Fatigue	1	Moderate	4
		Lethargy	1	Moderate	4
		Muscular weakness	1	Moderate	4
		Irritability	2	Moderate	3
	F, 13	Fatigue	1	Severe	3
	F, 9**	Drug rash	11	Mild	12
	F, 15**	Bipolar disorder	21	Severe	12
	M, 15	Stomach discomfort	4	Severe	6
	M, 13	Orthostatic	4	Severe	1

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	M, 15	hypotension Blood pressure increased	5	Severe	2
		Tachycardia	5	Severe	2
Placebo	F, 16	Bipolar disorder	5	Moderate	Unknown
	F, 15	Sedation	11	Moderate	12
	M, 17**	Bipolar disorder	10	Severe	4
	M, 10	Hostility	4	Severe	Unknown

From Sponsor Table 50 in Clinical Study Report

\*investigator term = slowed thinking

\*\*Same patient as listed in Table 32

In Study 150, Forty subjects (10.5%) discontinued due to adverse events. These 40 patients experienced 62 adverse events. Approximately 40% (25/62) of these adverse events (were potentially related to the underlying disorder (aggression, agitation, bipolar disorder, delusion, hallucination, irritability, psychotic disorder, schizophrenia).

Table 36. Discontinuations due to Adverse Events of Interest – Study 150

Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)
M, 13	Tachycardia	21	Moderate	15
	Angina pectoris	29	Mild	4
	Hyperhydrosis	29	Moderate	7
F, 16	Syncope	34	Severe	1
M, 17	Blood glucose incr.	96	Severe	Unknown
	HbA1c incr.	96	Severe	Unknown
M, 13	Extrasystoles	21	Severe	Unknown
	Angina pectoris	21	Severe	1
M, 13	Dyspnea	21	Severe	1
	Tachycardia	21	Severe	1
F, 14	Pulmonary hypertension	84	Mild	40
M, 10	Hypertension	81	Moderate	Unknown
M, 14	Overdose	181	Severe	1
M, 10	Neutropenia	28	Severe	29
F, 12	Tachycardia	3	Severe	7
M, 17	Petit mal epilepsy	142	Moderate	Unknown
M, 16	Sinus tachycardia	91	Mild	29
	Tachycardia paroxysmal	112	Moderate	Unknown

From Sponsor Table 11.3.5.2 in Clinical Study Report for Study 150

\*\*Same patient as listed in Table 33

### 7.3.4 Significant Adverse Events

A review of the adverse events in Studies 112, 149 and 150 did not reveal any significant events not included under deaths, serious adverse events or discontinuations due to adverse events.

### 7.3.5 Submission Specific Primary Safety Concerns

Several safety concerns have been identified in the adult clinical trials programs for quetiapine as well as for atypical antipsychotics in general, many of which are covered in the respective sections of this clinical review. Known potential safety signals include neutropenia, orthostatic hypotension, weight gain, hyperlipidemia, hyperglycemia, hypothyroidism, EPS and tardive dyskinesia, development of cataracts and suicidality (class effect associated with antidepressants in certain age groups).

#### *Cataracts*

A slit-lamp examination by an ophthalmologist was to be performed at entry into the open-label extension study (Study 150) and at the end of this 26-week study. The Sponsor provided these data only as categorical shifts in eye examination (normal to abnormal) in the submission. For patients who received placebo in Studies 112 and 149 and then received open-label quetiapine in Study 150, 2/129 (6.3%) had a shift from normal to abnormal eye examination (5 patients had abnormal eye exam at baseline that remained in this category). For patients who received quetiapine in Studies 112 and 149 and then received open-label quetiapine in Study 150, 1/251 (1%) had a shift from normal to abnormal eye examination (15 patients had abnormal eye exams at baseline that remained in this category). The Sponsor has been asked to provide more detailed clinical information regarding the shifts from normal to abnormal eye exams as well as the abnormal eye exams at baseline and end of study (same abnormalities noted?).

#### *Extrapyramidal Side Effects and Tardive Dyskinesia*

Though the Barnes Akathisia Scale and the Simpson Angus Scale were used to assess extrapyramidal side effects, adverse effects associated with EPS can also be noted in adverse event reporting. The following table summarizes the incidence of adverse events potentially associated with EPS. In Study 112, EPS occurred at > twice the rate in the quetiapine groups compared to placebo. In Study 149, rates of EPS were low and slightly greater than placebo.

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Table 37. Adverse Event Terms Potentially Related to EPS – Studies 112 and 149

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 75
<b>Study 112</b>			
Total*	<b>9 (12.3%)*</b>	<b>10 (13.5%)*</b>	<b>4 (5.3%)*</b>
Akathisia	3 (4.1%)	3 (4.1%)	2 (2.7%)
Dykinesia	2 (2.7%)	0	0
Extrapyramidal disorder	1 (1.4%)	1 (1.4%)	0
Hypokinesia	1 (1.4%)	1 (1.4%)	0
Muscle rigidity	2 (2.7%)	0	0
Musculoskeletal stiffness	1 (1.4%)	0	0
Psychomotor hyperactivity	0	1 (1.4%)	1 (1.3%)
Restlessness	1 (1.4%)	1 (1.4%)	0
Salivary hypersecretion	2 (2.7%)	2 (2.7%)	2 (2.7%)
Tremor	3 (4.1%)	3 (4.1%)	2 (2.7%)
	Quetiapine 400 mg/day N = 95	Quetiapine 600 mg/day N = 98	Placebo N = 90
<b>Study 149</b>			
Total*	<b>4 (4.2%)</b>	<b>3 (3.1%)</b>	<b>1 (1.1%)</b>
Akathisia	1 (1.1%)	1 (1%)	0
Dykinesia	0	0	0
Extrapyramidal disorder	0	0	0
Hypokinesia	0	0	0
Muscle rigidity	0	0	0
Musculoskeletal stiffness	1 (1.1%)	3 (3.1%)	1 (1.1%)
Psychomotor hyperactivity	0	0	0
Restlessness	1 (1.1%)	1 (1%)	0
Salivary hypersecretion	0	0	0
Tremor	2 (2.1%)	1 (1%)	1 (1.1%)

Modified from Sponsor table 49 (Study 112) and Table 51 (Study 149), added AE terms salivary hypersecretion and musculoskeletal stiffness from Table 11.3.2.4.1 (Study 112) and Table 11.3.2.4 (Study 149) in Clinical Study Reports

\*Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Since this reviewer added the AEs salivary hypersecretion and musculoskeletal stiffness, it is not known if these occurred in patients not already counted in the total tally by Sponsor, the overall incidence may be slightly higher if these occurred in unique patients.

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Table 38. Categorical Change from Baseline to End of Study in Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BAS) and AIMS\*

	Improved	No Change	Worsened
Study 112 SAS			
Quetiapine 400	21.8%	65.5%	12.7%
Quetiapine 800	21.8%	61.8%	16.4%
Placebo	23.8%	69.0%	7.1%
Study 149 SAS			
Quetiapine 400	12%	81.3%	6.7%
Quetiapine 800	7.4%	77.8%	14.8%
Placebo	19.4%	70.1%	10.4%
Study 112 BAS			
Quetiapine 400	9.1%	85.5%	5.5%
Quetiapine 800	3.6%	94.5%	1.8%
Placebo	9.5%	85.7%	4.8%
Study 149 BAS			
Quetiapine 400	8.0%	86.7%	5.3%
Quetiapine 800	6.2%	87.7%	6.2%
Placebo	9.0%	86.6%	4.5%
Study 112 AIMS			
Quetiapine 400	7.3%	85.5%	7.3%
Quetiapine 800	18.2%	80.0%	1.8%
Placebo	9.5%	88.1%	2.4%
Study 149 AIMS			
Quetiapine 400	13.3%	86.7%	0
Quetiapine 800	12.3%	85.2%	2.5%
Placebo	10.4%	89.6%	0

From Sponsor Tables 62, 63, 65 and X in Clinical Study Report (Study 112) and Tables 65, 66, 67 in Clinical Study Report (Study 149).  
 \*improved: < 1 change in total score, worsened: ≥ 1 change in total score

For the AIMS-7 analysis In Study 150, 20/380 (5.3%) of patients had improvements, 332/380 (88.8%) had no change and 22/380 (5.9%) had worsening.

*Suicidality Assessment*

The Sponsor conducted an in-house review of suicidal behavior and ideation in Studies 112, 149 and 150 following the process developed by the group at Columbia University. A group of Sponsor certified physicians who were not associated with these studies reviewed the identified events from the 3 studies. All study data were blinded to the reviewers except as provided in the narratives used for patient classification. No patients committed suicide during any of the clinical studies.

Table 39 (Sponsor's Table). Incidence of Patients with Suicidal Behavior/Ideation in Studies 112 and 149, Columbia-type Analysis

Classification (codes)	All patients		Age ≤12 years		Age 13 to 17 years	
	PLA (N=165)	QTP (N=340)	PLA (N=36)	QTP (N=85)	PLA (N=129)	QTP (N=255)
Suicidal behavior/ideation (1, 2, 3, 4)	0	5 (1.5)	0	3 (3.5)	0	2 (0.8)
-- Suicidal behavior (1, 2, 3)	0	2 (0.6)	0	2 (2.4)	0	0
-- Suicidal ideation (4)	0	3 (0.9)	0	1 (1.2)	0	2 (0.8)
Possible suicidal behavior/ideation (5, 6, 9) <sup>a</sup>	2 (1.2)	6 (1.8)	0	2 (2.4)	2 (1.6)	4 (1.6)

From Sponsor Table SU3 in Suicidality Report document

Category 5 = self-injurious behavior, intent unknown; category 6 = not enough information, death; category 9 = not enough information, non-death

The relative risk for suicidal behavior/ideation was calculated and is presented in Table 40. Each of the confidence interval comparisons between quetiapine and placebo included 1 and therefore not considered statistically significant.

Table 40 (Sponsor Table). Suicidal Behavior/ideation Relative Risk for Quetiapine Compared to Placebo in Studies 112 and 149 (pooled), Columbia-type Analysis

Classification (codes)	All patients		Age ≤12 years		Age 13 to 17 years	
	RR	95% CI	RR	95% CI	RR	95% CI
Suicidal behavior/ideation (1, 2, 3, 4)	2.91 <sup>a</sup>	0.352 – 24.080	3.01 <sup>a</sup>	0.160 – 56.855	2.57 <sup>a</sup>	0.125 – 52.810
Suicidal behavior/ideation (1, 2, 3, 4) + possible suicidal behavior/ideation (5, 6, 9) <sup>a</sup>	1.67	0.395 – 7.093	4.73 <sup>a</sup>	0.269 – 83.410	1.26	0.292 – 5.460

From Sponsor Table SU4 in Suicidality Report document

In Study 150 (open-label study), 14 patients with events possibly related to suicidality were identified: 5 patients with suicidal behavior/ideation and 9 patients with possibly suicidal events.

*Emergent Depression (Study 149)*

The incidence of emergent depression was assessed in Study 149 and defined as a CDRS-R (Children's Depression Rating Scale-Revised) total score ≥ 40 at Day 21 for patients whose baseline CDRS-R score was < 40. The incidence of emergent depression was 2.1% in the quetiapine 400 mg/day group, 1.0% in the quetiapine 600 mg/day group and 3.3% in the placebo group.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The most commonly reported adverse events (> 5% in either quetiapine dose group) for Study 112 are listed in Table 41. The Sponsor was asked to calculate the frequency of occurrence of somnolence + sedation since these are very similar adverse events. The Sponsor indicated that somnolence/sedation occurred in 32.9% (24/73) patients in the quetiapine 400 mg/day group, 35.1% (26/74) patients in the quetiapine 800 mg/day group and 10.7% (8/75) patients in the placebo group.

A dose-related signal for frequency of common adverse events appears likely for dizziness, dry mouth, and tachycardia.

Table 41. (Sponsor Table 45) Most Commonly Reported Adverse Events (> 5% in either quetiapine group) – Study 112

Preferred term	Quetiapine 400 mg/day (N=73)		Quetiapine 800 mg/day (N=74)		Placebo (N=75)	
	n	%	n	%	n	%
Somnolence	20	27.4	22	29.7	5	6.7
Headache	6	8.2	16	21.6	14	18.7
Dizziness	6	8.2	11	14.9	4	5.3
Dry mouth	3	4.1	7	9.5	1	1.3
Insomnia	9	12.3	7	9.5	17	22.7
Agitation	6	8.2	6	8.1	10	13.3
Tachycardia	4	5.5	6	8.1	0	
Increased appetite	3	4.1	5	6.8	3	4.0
Fatigue	4	5.5	4	5.4	3	4.0
Irritability	2	2.7	4	5.4	0	
Nausea	3	4.1	4	5.4	13	17.3
Sedation	4	5.5	4	5.4	3	4.0
Vomiting	3	4.1	4	5.4	6	8.0
Anxiety	4	5.5	3	4.1	5	6.7
Diarrhea	4	5.5	1	1.4	4	5.3

Sponsor Table 45 from Clinical Study Report

The most commonly reported adverse events (> 5% in either quetiapine dose group) for Study 149 are listed in Table 42. The Sponsor was asked to calculate the frequency of occurrence of somnolence + sedation since these are very similar adverse events. The Sponsor indicated that somnolence/sedation occurred in 49.5% (47/95) patients in the quetiapine 400 mg/day group, 57.1% (56/98) patients in the quetiapine 800 mg/day group and 14.4% (13/90) patients in the placebo group.

A dose-related signal for frequency of common adverse events appears likely for somnolence/sedation, nausea, and tachycardia.

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Table 42. (Sponsor Table 46) Most Commonly Reported Adverse Events (> 5% in either quetiapine group) – Study 149

Preferred term	Quetiapine 400 mg (N=95)		Quetiapine 600 mg (N=98)		Placebo (N=90)	
	n	%	n	%	n	%
Somnolence	27	28.4	31	31.6	9	10.0
Sedation	22	23.2	25	25.5	4	4.4
Dizziness	18	18.9	17	17.3	2	2.2
Headache	15	15.8	13	13.3	14	15.6
Nausea	6	6.3	10	10.2	4	4.4
Fatigue	13	13.7	9	9.2	4	4.4
Increased appetite	9	9.5	9	9.2	1	1.1
Tachycardia	5	5.3	8	8.2	0	
Vomiting	8	8.4	7	7.1	3	3.3
Dry mouth	7	7.4	7	7.1	0	
Weight increased	6	6.3	6	6.1	0	
Nasal congestion	3	3.2	6	6.1	2	2.2
Irritability	3	3.2	5	5.1	1	1.1

The most commonly reported adverse events were tabulated by age cohort (Study 112 did not enroll patients < 13 years). For patients 10 - 12 years, adverse events of increased appetite, dry mouth, tachycardia, weight increased and nasal congestion occurred more commonly compared to patients 13 to 17 years of age.

Table 43. Most Commonly Reported Adverse Events (> 5% in either quetiapine group) By Age Cohort – Studies 112 and 149 pooled

	10 - 12 Years		13 - 17 Years	
	Quetiapine N = 85	Placebo N = 36	Quetiapine N = 255	Placebo N = 129
Somnolence	24 (28.2)	2 (5.6)	76 (29.8)	12 (9.3)
Sedation	19 (22.4)	0	36 (14.1)	7 (5.4)
Dizziness	15 (17.6)	2 (5.6)	37 (14.5)	4 (3.1)
Headache	16 (18.8)	6 (16.7)	34 (13.3)	22 (17.1)
Fatigue	8 (9.4)	2 (5.6)	22 (8.6)	5 (3.9)
Increased appetite	12 (14.1)	0	14 (5.5)	4 (3.1)
Dry mouth	8 (9.4)	0	16 (6.3)	1 (0.8)
Insomnia	3 (3.5)	5 (13.9)	20 (7.8)	19 (14.7)
Nausea	6 (7.1)	1 (2.8)	17 (6.7)	16 (12.4)
Tachycardia	8 (9.4)	0	15 (5.9)	0
Vomiting	8 (9.4)	0	14 (5.5)	9 (7.0)
Agitation	4 (4.7)	5 (13.9)	15 (5.9)	11 (8.5)
Weight increased	6 (7.1)	0	11 (4.3)	2 (1.6)
Nasal congestion	5 (5.9)	1 (2.8)	4 (1.6)	2 (1.6)

From Sponsor Table SA01 from Summary-Clin-Safety document

## **7.4.2 Laboratory Findings**

### **7.4.2.1 Clinical Chemistry**

Per request of the Division, the Sponsor provided a separate submission addressing the metabolic effects of quetiapine on adult and pediatric/adolescent patients in their clinical trials database. These data, while also summarized briefly in this review, will be more extensively evaluated in a separate review document and will also evaluate the dose-response relationship to these metabolic effects.

#### *Mean Change Analyses*

The mean change analyses in the quetiapine treated patients for Studies 112 and 149 did not reveal any new findings. Mean increases were noted for AST, ALT, alkaline phosphatase, total cholesterol, LDL, and triglycerides. Interestingly, mean change in glucose was a decrease in Study 112 and an increase in Study 149, presumably related to prior antipsychotics with effects on glucose that may have elevated baseline values in Study 112. Similarly, prolactin concentrations decreased in Study 112 and increased in Study 149. The effects on TSH were variable within and between the two studies while the overall effect on free T4 and total T4 was a mean decrease.

Table 44. Clinical Chemistry Changes from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day (N=73)			Quetiapine 800 mg/day (N=74)			Placebo (N=75)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
AST (IU/L)	61	3.2459	11.33822	59	-0.8136	14.21082	63	-1.8889	9.80637
ALT (IU/L)	61	4.2787	18.15868	59	1.2373	25.38214	63	-1.4444	18.23925
Alkaline phosphatase (IU/L)	62	3.9194	20.51493	60	7.3500	21.37068	63	0.2857	26.07955
Total bilirubin (mg/dL)	62	-0.0871	0.21231	59	-0.1034	0.36998	63	0.0492	0.23201
Creatinine (mg/dL)	62	-0.0026	0.08402	59	0.0083	0.09952	63	0.0048	0.10690
BUN (mg/dL)	62	0.1129	3.50692	60	-0.1500	2.95058	63	0.0159	3.20026
Glucose (fasting) <sup>a</sup> (mg/dL)	68	-0.0735	12.07602	70	-1.4000	9.08000	67	-1.7015	10.82368
HOMA-R	56	1.1112	5.56351	57	0.0897	3.97753	56	-0.4368	6.11830
Insulin (µIU/mL)	62	4.2742	19.25938	59	1.2203	17.29567	60	-1.0333	19.05742
HbA1c (%)	62	0.0210	0.22480	62	0.0645	0.22477	61	-0.0049	0.25194
QUICKI	56	-0.0075	0.04560	57	-0.0056	0.03690	56	0.0062	0.04255
Bicarbonate (mEq/L)	58	0.4138	2.38441	56	-0.2857	3.20632	61	-0.4754	3.36950
Chloride (mEq/L)	62	0.4677	2.75632	60	0.1500	2.93907	63	1.1111	2.89109
Potassium (mEq/L)	62	-0.0113	0.41136	59	0.0458	0.47282	63	-0.0524	0.48422
Sodium (mEq/L)	62	0.5161	2.85003	60	-0.1167	2.89998	63	0.6984	3.14507
Total cholesterol (mg/dL)	62	7.8226	28.82310	59	7.4237	24.65710	63	-8.0635	25.74745
HDL (mg/dL)	62	-2.8226	9.24267	60	-0.9667	9.90115	63	-2.4603	8.95297
LDL (mg/dL)	62	8.6613	22.73579	60	4.8167	21.78515	63	-3.8889	20.50500
Triglycerides (mg/dL)	62	9.6613	64.77172	60	15.5833	47.94357	63	-8.1587	59.39730
TSH (µIU/mL)	62	0.3734	1.35773	59	-0.0966	0.93745	62	-0.0395	1.08274
Free T4 (ng/dL)	62	-0.1510	0.18939	60	-0.2790	0.23064	63	0.0097	0.21324
Total T4 (µg/dL)	62	-1.4419	1.29508	60	-2.5083	1.90897	63	0.1063	1.21667
Triiodothyronine resin uptake (%)	62	-0.9032	3.60650	60	0.7333	4.36421	63	-0.1746	4.45964
Prolactin (ng/mL)	63	-10.5476	16.12225	60	-7.8333	26.47357	63	-18.2467	28.74950

From Sponsor Table 53 from Clinical Study Report (Study 112)

Table 45. Clinical Chemistry Mean Changes from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg (N=95)			Quetiapine 600 mg (N=98)			Placebo (N=90)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
AST (IU/L)	90	1.8111	7.94771	87	2.5977	11.65937	79	1.1519	5.54952
ALT (IU/L)	90	3.0444	11.67049	87	6.6322	21.31225	79	0.4051	9.78424
Alkaline phosphatase (IU/L)	90	1.8111	26.24298	87	-4.0000	27.09758	79	-10.3038	36.42180
Total bilirubin (mg/dL)	90	-0.0700	0.17639	87	-0.1195	0.22968	79	0.0051	0.28189
Creatinine (mg/dL)	90	0.0133	0.08506	87	0.0195	0.15238	79	0.0139	0.09836
BUN (mg/dL)	90	-0.2111	3.35366	87	-0.8736	3.04541	79	0.7215	3.38525
Glucose (fasting) <sup>a</sup> (mg/dL)	87	3.4828	11.49708	83	3.7590	13.10240	81	-1.1728	11.03040
HOMA-R	67	1.9501	12.35612	73	2.8898	7.02099	67	-0.0210	3.77324
Insulin (μIU/mL)	76	6.7500	46.00409	83	10.5060	26.58093	76	-1.3816	23.88750
HbA1c (%)	88	-0.0011	0.25708	85	0.0494	0.23023	81	0.0123	0.16154
QUICKI	67	-0.0115	0.03723	73	-0.0197	0.04365	67	0.0006	0.04381
Bicarbonate (mEq/L)	90	-0.0667	3.12223	85	-0.6706	3.08756	76	-0.5132	2.99107
Chloride (mEq/L)	90	0.7778	2.69322	87	1.0460	2.90512	79	0.2405	2.47664
Potassium (mEq/L)	90	-0.0200	0.40090	87	-0.0460	0.48412	79	-0.1215	0.45083
Sodium (mEq/L)	90	0.7444	2.77857	87	0.3103	3.55459	79	-0.4557	2.78640
Total cholesterol (mg/dL)	90	7.8111	23.84166	87	7.6092	22.60806	79	-3.3291	23.88633
HDL (mg/dL)	90	-0.0556	7.72907	87	-1.4253	7.56773	79	-1.0380	7.95733
LDL (mg/dL)	90	5.6444	21.29109	87	2.8851	19.02106	79	-0.4810	18.51878
Triglycerides (mg/dL)	90	11.1667	58.53900	87	30.5747	64.59023	79	-8.7342	60.11095
TSH (μIU/mL)	81	-0.1063	1.18757	85	0.1973	1.11985	80	-0.1070	1.10592
Free T4 (ng/dL)	82	-0.1646	0.15178	86	-0.1659	0.17034	82	-0.0033	0.15101
Total T4 (μg/dL)	82	-1.4317	1.32338	86	-1.7733	1.57042	82	0.0207	1.20756
Triiodothyronine resin uptake (%)	82	-0.2805	3.11616	86	0.7558	3.64590	82	0.3171	3.59999
Prolactin (ng/mL)	82	2.8378	13.28464	86	1.8640	11.25527	82	-1.1451	9.17482

From Sponsor Table 57 from Clinical Study Report (Study 149)

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 NDA 20-639 SE5-045 & SE5-046  
 Seroquel (quetiapine fumarate)

Table 46. Clinical Chemistry Mean Changes from Baseline to Final Visit (Study 150)

	Bipolar I Disorder (N=205)			Schizophrenia (N=175)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
<b>Total</b>									
AST (IU/L)	172	-2.4477	18.8705	160	1.7175	24.6534	332	-0.4404	21.9151
ALT (IU/L)	172	-2.6047	17.2113	160	-2.7681	24.2469	332	-2.6834	20.8676
Alkaline phosphatase (IU/L)	172	2.6628	50.0356	161	-1.0168	44.1889	333	0.8838	47.2643
Total bilirubin (mg/dL)	172	0.0081	0.2047	161	-0.0197	0.4025	333	-0.0053	0.3160
Creatinine (mg/dL)	172	0.0301	0.1033	161	0.0395	0.1200	333	0.0347	0.1117
BUN (mg/dL)	172	-0.1163	3.7570	160	0.2500	3.2852	332	0.0602	3.5369
Glucose (fasting) <sup>a</sup> (mg/dL)	173	0.0925	13.1464	161	5.2931	25.1642	334	2.5994	20.0075
HOMA-R	146	-0.4460	9.4470	156	0.9910	8.8029	302	0.2963	9.1331
Insulin (μIU/mL)	159	-1.8302	36.6648	158	1.9620	25.1355	317	0.0599	31.4588
HbA1c (%)	172	0.0262	0.2395	160	0.0936	0.6796	332	0.0586	0.5026
QUICKI	146	-0.0004	0.0414	156	-0.0012	0.0422	302	-0.0008	0.0417
Bicarbonate (mEq/L)	170	-0.4000	3.3413	156	-1.1923	3.2211	326	-0.7791	3.3032
Chloride (mEq/L)	172	-0.3023	3.2103	159	0.2013	2.9312	331	-0.0604	3.0851
Potassium (mEq/L)	172	-0.0349	0.4853	160	-0.0526	0.4319	332	-0.0434	0.4597
Sodium (mEq/L)	172	-0.6279	3.5212	160	-0.1825	2.9583	332	-0.4133	3.2648
Total cholesterol (mg/dL)	173	-4.4104	23.0744	161	-0.4850	28.1526	334	-2.5182	25.6842
HDL (mg/dL)	173	-2.7110	8.2249	161	-0.5940	8.6012	334	-1.6905	8.4623
LDL (mg/dL)	173	-2.4220	21.1419	160	-0.1750	23.5883	333	-1.3423	22.3451
Triglycerides (mg/dL)	173	3.6185	70.1192	161	-0.1148	68.0005	334	1.8189	69.0277
TSH (μIU/mL)	170	0.0339	1.3367	157	0.3223	1.2095	327	0.1724	1.2834
Free T4 (ng/dL)	173	0.0254	0.1870	160	0.0071	0.2116	333	0.0166	0.1991
Total T4 (μg/dL)	173	-0.0225	1.5781	160	-0.0988	1.7341	333	-0.0592	1.6528
Triiodothyronine resin uptake (%)	173	0.3295	3.5374	160	0.2454	3.4681	333	0.2891	3.4992
Prolactin (ng/mL)	173	-2.2439	10.8011	161	0.4516	13.8392	334	-0.9446	12.4138

From Sponsor Table 45 in Clinical Study Report (Study 150)

*Prolactin*

The effect of quetiapine on prolactin was evaluated by gender and by age cohort for Study 149 (since Study 112 had decrements in prolactin at endpoint). Overall, male patients had a greater elevation in prolactin compared to females. Analysis by age revealed similar elevations in prolactin across 3 different cohorts – the 16 to 17 year cohort had variable effects between quetiapine doses.

Table 47. Mean Change from Baseline in Prolactin By Gender (Study 149)

	Quetiapine 400	Quetiapine 600	Placebo
Male			
N	39	51	50
Mean Change	3.8	2.8	0.49
Female			
N	43	35	32
Mean Change	1.9	0.53	-3.7

From Sponsor Table 11.3.7.3.6.3.2 in Clinical Study Report (149)

Table 48. Mean Change from Baseline in Prolactin By Age (Study 149)

	Quetiapine 400	Quetiapine 600	Placebo
10 - 12 years			
N	37	38	32
Baseline	7.8	7.4	7.5
End of Study	10.9	9.3	5.9
Mean Change	2.7	1.9	-1.9
13 to 15 years			
N	33	35	30
Baseline	11.3	7.8	10.7
End of Study	14.5	10.7	9.9
Mean Change	2.3	3.6	-1.3
16 to 17 years			
N	12	13	20
Baseline	9.5	14.1	9.3
End of Study	14.8	12.7	9.2
Mean Change	4.7	-3.1	0.26

From Sponsor Table 11.3.7.3.6.3.1 in Clinical Study Report (149)

## Outlier Analyses

A table of Sponsor-defined potentially clinically important values is included in Appendix 9.7. The most significant shifts to high occurred with triglycerides (Studies 112 and 149) and prolactin (Study 149).

Table 49. Clinically Important Shifts from Baseline to the Final Visit (Study 112)\*

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 73	QTP 800 N = 74	PC N = 75	QTP 400 N = 73	QTP 800 N = 74	PC N = 75
Glucose (fasting) [mg/dL]	0	0	0	1 (1.5)	0	0
Bicarbonate (mEq/L)	0	1 (1.9)	4 (6.7)	0	0	0
Potassium (mEq/L)	0	0	1 (1.6)	0	0	1 (1.6)
Total cholesterol (mg/dL)	NA	NA	NA	2 (3.3)	0	1 (1.6)
HDL (mg/dL)	8 (14.8)	8 (16)	9 (16.7)	NA	NA	NA
LDL (mg/dL)	NA	NA	NA	1 (1.7)	1 (1.7)	1 (1.6)
Triglycerides (mg/dL)	NA	NA	NA	5 (8.9)	1 (1.8)	1 (1.7)
TSH (μIU/ml)	NA	NA	NA	3 (4.9)	0	0
Free T4 (ng/dL)	0	2 (3.3)	0	0	0	0
Total T4 (ng/dL)	2 (3.2)	3 (5.0)	0	0	0	0
Prolactin (ng/mL)	NA	NA	NA	1 (2.4)	3 (7.5)	1 (2.8)

From Sponsor Table 56 in Clinical Study Report (Study 112)

\*There were no shifts to low or high for AST, ALT, alkaline phosphatase, total bilirubin, creatinine, HbA1c, chloride, sodium, T3 uptake.  
 NA = not applicable, no clinically important values were defined

Table 50. Clinically Important Shifts from Baseline to the Final Visit (Study 149)\*

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 95	QTP 600 N = 98	PC N = 90	QTP 400 N = 95	QTP 600 N = 98	PC N = 90
Creatinine (mg/dL)	NA	NA	NA	0	1 (1.2)	0
Glucose (fasting) [mg/dL]	0	0	0	1 (1.1)	1 (1.2)	0
Bicarbonate (mEq/L)	6 (6.7)	4 (4.9)	5 (6.8)	0	2 (2.4)	0
Potassium (mEq/L)	0	0	0	1 (1.1)	1 (1.2)	1 (1.3)
Sodium (mEq/L)	0	1 (1.2)	0	0	0	0
Total cholesterol (mg/dL)	NA	NA	NA	0	3 (3.5)	1 (1.3)
HDL (mg/dL)	2 (2.6)	13 (16.9)	4 (6.6)	NA	NA	NA
LDL (mg/dL)	NA	NA	NA	0	1 (1.2)	0
Triglycerides (mg/dL)	NA	NA	NA	6 (7.5)	12 (14.3)	4 (5.7)
TSH (μIU/ml)	NA	NA	NA	2 (2.6)	2 (2.4)	1 (1.3)
Free T4 (ng/dL)	1 (1.2)	0	0	0	0	0
Total T4 (ng/dL)	0	3 (3.5)	0	0	0	0
Prolactin (ng/mL)	NA	NA	NA	12 (15.8)	10 (12.3)	2 (2.6)

From Sponsor Table 59 in Clinical Study Report (Study 149)

\*There were no shifts to low or high for AST, ALT, alkaline phosphatase, total bilirubin (one shift to high in PC group), BUN (2 shifts to high in PC group), insulin, HbA1c, chloride, T3 uptake.  
 NA = not applicable, no clinically important values were defined

Table 51. Clinically Important Shifts from Baseline to the Final Visit (Study 150)\*

	Shift to Low, n (%)			Shift to High, n (%)		
	Bipolar Disorder (N = 205)	Schizophrenia (N = 175)	Total (N = 380)	Bipolar Disorder (N = 205)	Schizophrenia (N = 175)	Total (N = 380)
AST	NA	NA	NA	0	1 (0.6)	1 (0.3)
ALT	NA	NA	NA	0	1 (0.6)	1 (0.3)
Total bilirubin	NA	NA	NA	0	1 (0.6)	1 (0.3)
BUN	0	0	0	3 (1.8)	2 (1.3)	5 (1.5)
Glucose (fasting) [mg/dL]	0	0	0	1 (0.6)	6 (3.8)	7 (2.1)
HbA1c	NA	NA	NA	0	2 (1.3)	2 (0.6)
Bicarbonate (mEq/L)	7 (4.4)	9 (5.9)	16 (5.1)	1 (0.6)	2 (1.3)	3 (1.0)
Potassium (mEq/L)	0	0	0	1 (0.6)	1 (0.6)	2 (0.6)
Sodium (mEq/L)	0	0	0	1 (0.6)	0	1 (0.3)
Total cholesterol (mg/dL)	NA	NA	NA	0	1 (0.6)	1 (0.3)
HDL (mg/dL)	19 (13.4)	21 (16.5)	40 (14.9)	NA	NA	NA
LDL (mg/dL)	NA	NA	NA	1 (0.6)	0	1 (0.3)
Triglycerides (mg/dL)	NA	NA	NA	18 (11.9)	13 (8.4)	31 (10.2)
TSH (μIU/ml)	NA	NA	NA	5 (3.0)	4 (2.6)	9 (2.8)
Free T4 (ng/dL)	0	1 (0.6)	1 (0.3)	0	0	0
Total T4 (ng/dL)	2 (1.2)	6 (3.8)	8 (2.5)	0	0	0
Prolactin (ng/mL)	NA	NA	NA	6 (3.9)	13 (8.7)	19 (6.3)

From Sponsor Table 47 from Clinical Study Report (Study 150)

\*There were no shifts to low or high for a kaline phosphatase, creatinine, chloride.

NA = not applicable, no clinically important values were defined

### Prolactin

Potentially clinically significant increases in prolactin concentration were defined as > 26 ng/ml for males and > 20 ng/ml for females.

For Study 149, 8 female patients had increased prolactin in the quetiapine groups compared to 0 patients in the placebo group.

Table 52. Distribution of Potentially Clinically Significant Shifts in Prolactin Concentration

	Female		Male	
	Quetiapine	Placebo	Quetiapine	Placebo
Study 149				
N	8	0	15	2
> 20 – 25 ng/ml	NA	NA	7 (47%)	1 (50%)
> 25 – 30 ng/ml	2 (25%)	0	3 (20%)	1 (50%)
> 30 – 35 ng/ml	4 (50%)	0	3 (20%)	0
> 35 – 40 ng/ml	1 (12.5%)	0	1 (7%)	0
> 40 – 45 ng/ml	1 (12.5%)	0	0	0
> 45 – 50 ng/ml	0	0	1 (7%)	0
Study 150				
N	9	NA	10	NA

For Study 112, only one female patient in the quetiapine group had a potentially clinically significant shift in prolactin to 131.5 ng/ml. Three male patients had shifts to high prolactin, the highest shift was to 40.9 ng/ml. One male patient in the placebo group had a shift to 50.8 ng/ml.

For Study 150, 19 patients had clinically important shifts to high prolactin. In the clinical study report, the Sponsor provided the prolactin data in mIU/L units and has been asked to resubmit the data in ng/ml so that the results can be compared across trials.

#### 7.4.2.2 Hematology

##### *Mean Change Analyses*

The mean change analyses did not reveal any new significant findings. Consistent with adult clinical data, a decrease in neutrophils was noted in both studies, though Study 149 findings were similar to placebo.

Table 53. Hematology Changes from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day (N=73)			Quetiapine 800 mg/day (N=74)			Placebo (N=75)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Hematocrit (%)	65	-0.4652	2.63873	66	-1.0227	2.48118	67	-0.2075	2.56079
Total RBC ( $10^6/\mu\text{L}$ )	64	-0.0844	0.27673	65	-0.1077	0.26179	67	-0.0328	0.31449
Hemoglobin (g/dL)	64	-0.2734	0.74456	66	-0.3561	0.73634	67	-0.0627	0.86407
Platelet count ( $10^3/\mu\text{L}$ )	63	7.0794	39.25159	65	-0.2308	52.12958	65	-1.9692	45.35415
Total WBC ( $10^3/\mu\text{L}$ )	64	0.1359	1.86483	65	-0.1754	1.93092	67	0.2433	2.50752
Basophils ( $10^3/\mu\text{L}$ )	65	0.0042	0.02030	64	0.0022	0.01647	66	-0.0055	0.02328
Eosinophils ( $10^3/\mu\text{L}$ )	65	0.0398	0.38102	65	0.0143	0.18580	66	-0.0073	0.18085
Lymphocytes ( $10^3/\mu\text{L}$ )	65	0.1445	0.58748	64	-0.0159	0.57026	66	0.0498	0.54092
Monocytes ( $10^3/\mu\text{L}$ )	64	0.0055	0.18085	64	-0.0141	0.21880	66	-0.0032	0.21826
Neutrophils ( $10^3/\mu\text{L}$ )	63	-0.0690	1.87248	64	-0.1167	1.93323	66	0.3550	2.53009

From Sponsor Table 50 in Clinical Study Report (Study 112)

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 Seroquel (quetiapine fumarate)

Table 54. Hematology Changes from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg (N=95)			Quetiapine 600 mg (N=98)			Placebo (N=90)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Hematocrit (volume fraction)	87	-1.1149	2.14999	83	-1.3193	2.42670	78	-0.2269	2.31890
Total RBC count (10 <sup>6</sup> /μL)	88	-0.1205	0.23933	85	-0.1341	0.26572	81	-0.0494	0.26178
Hemoglobin (g/dL)	88	-0.3341	0.71998	85	-0.3871	0.74014	80	-0.1688	0.72314
Platelet count (10 <sup>3</sup> /μL)	88	-8.3523	39.08289	85	6.5176	41.95962	81	0.1728	47.08338
Total WBC count (10 <sup>3</sup> /μL)	88	-0.2727	1.86318	85	-0.1224	1.51715	81	-0.0444	1.94885
Basophils (10 <sup>3</sup> /μL)	88	-0.0003	0.02996	83	0.0014	0.02405	80	0.0039	0.02844
Eosinophils (10 <sup>3</sup> /μL)	88	0.0269	0.16036	83	0.0370	0.11892	80	0.0151	0.09917
Lymphocytes (10 <sup>3</sup> /μL)	88	-0.1931	0.51573	83	-0.1683	0.52391	80	0.0469	0.44298
Monocytes (10 <sup>3</sup> /μL)	88	0.0194	0.15260	83	0.0101	0.16217	80	0.0000	0.15929
Neutrophils (10 <sup>3</sup> /μL)	88	-0.1242	1.64769	83	-0.0192	1.26954	80	-0.1013	1.77366

From Sponsor Table 54 in Clinical Study Report (Study 149)

Table 55. Hematology Changes from Baseline to Final Visit (Study 150)

	Bipolar I Disorder (N=205)			Schizophrenia (N=175)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
<b>Total</b>									
Hematocrit (%)	187	-0.0925	2.4192	158	0.1001	2.9079	345	-0.0043	2.6520
Total RBC (10 <sup>6</sup> /μL)	188	0.0043	0.3006	163	0.2050	0.3132	351	0.0139	0.3062
Hemoglobin (g/dL)	188	-0.0495	0.7843	163	0.0542	0.9650	351	-0.0013	0.8731
Platelet count (10 <sup>3</sup> /μL)	188	-3.8298	36.2726	159	5.5836	52.3841	347	0.4836	44.5672
Total WBC (10 <sup>3</sup> /μL)	188	-0.0441	1.4754	163	-0.0471	2.2804	351	-0.0455	1.8894
Basophils (10 <sup>3</sup> /μL)	186	-0.0034	0.0254	161	0.0043	0.0243	347	0.0002	0.0252
Eosinophils (10 <sup>3</sup> /μL)	186	-0.0446	0.1839	159	-0.0487	0.2140	345	-0.0465	0.1981
Lymphocytes (10 <sup>3</sup> /μL)	186	-0.0054	0.4574	161	0.0761	0.4993	347	0.0324	0.4784
Monocytes (10 <sup>3</sup> /μL)	186	-0.0267	0.1473	161	-0.0176	0.1786	347	-0.0225	0.1624
Neutrophils (10 <sup>3</sup> /μL)	186	0.0331	1.2954	161	-0.0302	2.1440	347	0.0037	1.7389

From Sponsor Table 43 from Clinical Study Report (Study 150)

### Outlier Analyses

Clinically important shifts from baseline to the final visit show similar % shifts to low ANC in the quetiapine and placebo groups. Clinically important shifts at any time in the study were available for Study 112 (Study 149 was a 3-week study with assessments at baseline and end of study), show similar % shifts to low ANC in the quetiapine and placebo groups. A table providing ANC values for these cases is in Appendix 9.8.

For the pooled analysis for studies 112 and 149, 3.5% (5/144) of patients in the placebo group had a shift in ANC to  $\leq 1.5 \times 10^9/L$  at any time compared to 4.8% (14/294) of patients in the quetiapine group. In the placebo group, 3.1% and 3.6% of patients had a shift to low ANC in the 10 - 12 years and 13 to 17 year age groups respectively. In the quetiapine group, 8.2% and 3.6% of patients had a shift to low ANC in these age cohorts (data from Sponsor Table SA04 in summary-clin-safety document).

Table 56. Clinically Important Shifts from Baseline to the Final Visit (Study 112)\*

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 73	QTP 800 N = 74	PC N = 75	QTP 400 N = 73	QTP 800 N = 74	PC N = 75
Hematocrit (%)	6 (10)	2 (3.4)	0	0	1 (1.7)	1 (1.6)
Hemoglobin (g/dL)	2 (3.2)	0	1 (1.5)	0	0	0
Total WBC ( $10^9/L$ )	0	0	0	1 (1.6)	1 (1.5)	1 (1.5)
Neutrophils ( $10^9/L$ )	2 (3.3)	1 (1.6)	2 (3.2)	1 (1.6)	1 (1.6)	3 (4.8)
Eosinophils ( $10^9/L$ )	NA	NA	NA	2 (3.3)	0	0

From Sponsor Table 52 from Clinical Study Report (Study112)

\*There were no shifts to low or high for total RBC, platelet count, basophils, lymphocytes, monocytes.

NA = not applicable, no clinically important values were defined

Table 57. Clinically Important Shifts At Any Time During the Study (Study 112)\*

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 73	QTP 800 N = 74	PC N = 75	QTP 400 N = 73	QTP 800 N = 74	PC N = 75
Hematocrit (%)	6 (8.2)	4 (5.4)	3 (4%)	0	2 (2.7)	1 (1.3)
Hemoglobin (g/dL)	3 (4.1)	1 (1.3)	1 (1.3)	-	-	-
Neutrophils ( $10^9/L$ )	5 (6.8)	2 (2.7)	6 (8%)	-	-	-

Sponsor provided data in text format

No shifts noted for RBC, platelets, WBC (low)

Table 58. Clinically Important Shifts from Baseline to the Final Visit (Study 149)\*

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 95	QTP 600 N = 98	PC N = 90	QTP 400 N = 95	QTP 600 N = 98	PC N = 90
Hematocrit (%)	0	7 (8.9)	1 (1.4)	1 (1.2)	0	2 (2.8)
Hemoglobin (g/dL)	2 (2.3)	2 (2.4)	0	0	0	0
Neutrophils ( $10^9/L$ )	3 (3.6)	4 (4.9)	2 (2.5)	0	0	0
Eosinophils ( $10^9/L$ )	NA	NA	NA	2 (2.3)	0	0

From Sponsor Table 56 in Clinical Study Report (Study 149)

\*There were no shifts to low or high for total RBC (one shift in PC group), WBC (one shift in PC group), basophils, lymphocytes, monocytes.

NA = not applicable, no clinically important values were defined

Table 59. Clinically Important Shifts from Baseline to the Final Visit (Study 150)\*

	Shift to Low, n (%)			Shift to High, n (%)		
	Bipolar Disorder N = 205	Schizophrenia N = 175	Total N = 380	Bipolar Disorder N = 205	Schizophrenia N = 175	Total N = 380
Hematocrit (%)	8 (4.7)	2 (1.4)	10 (3.1)	1 (0.6)	3 (2.1)	4 (1.3)
Hemoglobin (g/dL)	2 (1.1)	1 (0.6)	3 (0.9)	1 (0.6)	3 (1.9)	4 (1.2)
Platelet count	0	0	0	0	1 (0.6)	1 (0.3)
Total WBC	0	0	0	0	1 (0.6)	1 (0.3)
Neutrophils (10 <sup>9</sup> /L)	6 (3.4)	2 (1.3)	8 (2.4)	0	2 (1.3)	2 (0.6)
Eosinophils (10 <sup>9</sup> /L)	NA	NA	NA	2 (1.1)	1 (0.6)	3 (0.9)

From Sponsor Table 44 in Clinical Study Report (Study 150)

\*There were no shifts to low or high for total RBC, basophils, lymphocytes, or monocytes.

NA = not applicable, no clinically important values were defined

A total of 27 (8.3%) of patients shifted to potentially clinically important low ANC at *any time* in the Study 150.

### 7.4.3 Vital Signs

Approximately 11-19% of patients took concomitant psychostimulants in Study 149 (comorbid ADHD). The Sponsor has been asked to provide additional vital signs analyses for the patients with and without concomitant psychostimulant use to further evaluate the safety signal. However, it should be noted that psychostimulants were not allowed in Study 112 and there were similar findings between the two studies with regard to vital sign changes.

### Mean Change Analyses

The mean change analyses for blood pressure and pulse revealed an increase in supine and standing pulse and systolic and diastolic blood pressure in the quetiapine groups compared to placebo. No overall effect consistent with orthostatic hypotension was noted in these trials (see Appendix 9.9).

Table 60. Vital Signs: Mean (SD) Change from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 75
Supine pulse (bpm)	6 (12.3)	3.9 (12.2)	-1.4 (11.3)
Supine Systolic BP (mmHg)	2 (10.3)	1 (9.7)	-1.6 (7.4)
Supine Diastolic BP (mmHg)	1.3 (8.4)	0.2 (12.4)	0.1 (8.5)
Standing Pulse (bpm)	6.3 (13.1)	2.2 (17.1)	-2.5 (13.1)
Standing Systolic BP (mmHg)	2.3 (10.8)	-0.4 (10.3)	-1.7 (9.1)
Standing Diastolic BP (mmHg)	2.1 (8.6)	1.1 (10.2)	-1.2 (7.7)

From Sponsor Table 59 in Clinical Study Report (Study 112)

Table 61. Vital Signs: Mean (SD) Change from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg/day n = 76*	Quetiapine 600 mg/day n = 81*	Placebo n = 68*
Supine pulse (bpm)	8.8 (13.6)	10.6 (16.3)	-0.8 (10.9)
Supine Systolic BP (mmHg)	0.4 (9.8)	2.4 (10.3)	-2.7 (8.9)
Supine Diastolic BP (mmHg)	1.3 (7.6)	3.1 (10.1)	1.0 (10.4)
Standing Pulse (bpm)	9.6 (15.2)	11.3 (18.9)	0.1 (12.7)
Standing Systolic BP (mmHg)	1.0 (11.5)	1.3 (9.6)	-0.8 (9.4)
Standing Diastolic BP (mmHg)	1.4 (11.6)	1.7 (10.1)	0.2 (9.3)

From Sponsor Table 63 in Clinical Study Report (Study 149)

\*Vital signs data available for this number of patients; safety population included n = 95, 98 and 90 for quetiapine 400, 600 and placebo groups

## Outlier Analyses

### *Shifts from Baseline to Final Visit*

A table of Sponsor-defined potentially clinically important values is included in Appendix 9.7. Significantly greater percentages of patients exhibited shifts to high pulse and systolic blood pressure in the quetiapine groups compared to placebo.

Table 62. Clinically Important Shifts in Vital Signs From Baseline to Final Visit (Study 112)

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 73	QTP 800 N = 74	PC N = 75	QTP 400 N = 73	QTP 800 N = 74	PC N = 75
Supine Pulse	0	0	0	1 (1.4)	2 (2.7)	0
Supine Systolic BP	3 (4.5)	3 (4.4)	2 (2.9)	5 (7.6)	3 (4.4)	1 (1.4)
Supine Diastolic BP	3 (4.3)	0	1 (1.4)	1 (1.4)	2 (2.9)	2 (2.9)
Standing Pulse	0	0	0	6 (8.7)	5 (7.4)	0
Standing Systolic BP	2 (3.1)	5 (7.9)	5 (7.5)	4 (6.2)	3 (4.8)	1 (1.5)
Standing Diastolic BP	0	1 (1.5)	1 (1.4)	7 (10)	5 (7.6)	6 (8.7)

From Sponsor Table 60 in Clinical Study Report (Study 112)

Table 63. Clinically Important Shifts in Vital Signs From Baseline to Final Visit (Study 149)

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 95	QTP600 N = 98	PC N = 90	QTP 400 N = 95	QTP 600 N = 98	PC N = 90
Supine Pulse	0	0	0	1 (1.1)	2 (2.2)	0
Supine Systolic BP	2 (2.4)	2 (2.3)	0	6 (7.1)	4 (4.5)	1 (1.3)
Supine Diastolic BP	0	0	2 (2.7)	1 (1.2)	4 (5.1)	3 (4.1)
Standing Pulse	0	0	0	13 (14.3)	10 (11.1)	1 (1.2)
Standing Systolic BP	3 (3.6)	6 (6.7)	2 (2.4)	9 (10.7)	2 (2.2)	4 (4.8)
Standing Diastolic BP	2 (2.6)	0	2 (2.7)	9 (11.5)	10 (12.0)	14 (18.7)

From Sponsor Table 64 in Clinical Study Report (Study 149)

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*Shifts at Any Time*

The Sponsor did not provide a similar summary table for standing vital signs and has been requested to provide these data. Consistent with Tables 62 and 63 above, the quetiapine groups were associated with significantly greater percentages of patients with elevations in supine pulse, systolic BP and diastolic BP.

Table 64. Clinically Important Shifts in Vital Signs At Any Time (Studies 112 and 149 Pooled)

	Shift	QTP N = 340			PC N = 165		
		N	n	%	N	n	%
Supine Pulse (bpm)	> 120	333	27	8.1	161	0	0
	≥ 15 increase	335	170	50.7	163	30	18.4
	< 50	334	1	0.3	161	2	1.2
	≥ 15 decrease	335	41	12.2	163	33	20.2
Supine Systolic BP (mmHg)	> 121*	317	45	14.2	153	9	5.9
	≥ 20 increase	335	51	15.2	163	9	5.5
	< 89*	325	29	8.9	157	10	6.4
	> 20 decrease	335	27	8.1	163	13	8.0
Supine Diastolic BP (mmHg)	≥ 78*	315	53	16.8	151	11	7.3
	≥ 10 increase	335	136	40.6	163	40	24.5
	≥ 30 increase	335	5	1.5	163	3	1.8
	≤ 52*	321	36	11.2	154	21	13.6
	> 20 decrease	335	32	9.6	163	9	5.5

\*Supine systolic BP: 10 to 12 years: boys > 123, girls > 121; 13-17 years: boys > 136, girls > 128; 10 to 12 years: ≤ 89; 13 to 17 years: ≤ 99  
 Supine diastolic BP: 10 to 12 years: ≥ 78; 13 to 17 years: boys ≥ 85, girls ≥ 82; 10 to 12 years ≤ 52, 13 to 17 years ≤ 56.  
 From Sponsor Table SA14 in Summary Clin Safety document

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 Seroquel (quetiapine fumarate)

An analysis for clinically important shifts in vital signs at any time by age cohort was performed. Patients 10 - 12 years of age have a greater frequency of clinically important shifts in vital signs except for supine pulse > 120 bpm (1.2% in patients < 12, 10.5% in patients 13-17 years of age). It is noteworthy that 60% of patients in the 10 - 12 years cohort have an increase in supine pulse of > 15 bpm compared to 0 patients in the placebo group for this same cohort.

Table 65. Clinically Important Shifts in Vital Signs At Any Time – By Age Cohort (Studies 112 and 149 Pooled)

	Shift	Quetiapine			PC		
		N	n	%	N	n	%
<b>10 - 12 Years</b>							
Supine Pulse (bpm)	> 120	85	1	1.2	36	0	0
	≥ 15 increase	85	51	60	36	0	0
Supine Systolic BP (mmHg)	> 121*	80	16	20	32	3	9.4
	≥ 20 increase	85	15	17.6	36	1	2.8
Supine Diastolic BP (mmHg)	≥ 78*	74	22	29.7	29	6	20.7
	≥ 10 increase	85	40	47.1	36	8	22.2
	≥ 30 increase	85	2	2.4	36	1	2.8
<b>13 – 17 Years</b>							
Supine Pulse (bpm)	> 120	248	26	10.5	125	0	0
	≥ 15 increase	250	119	47.6	127	30	23.6
Supine Systolic BP (mmHg)	> 128*	237	29	12.2	121	6	5
	≥ 20 increase	250	36	14.4	127	8	6.3
Supine Diastolic BP (mmHg)	≥ 82*	241	31	12.9	122	5	4.1
	≥ 10 increase	250	96	38.4	127	32	25.2
	> 30 increase	250	3	1.2	127	2	1.6

\*Supine systolic BP: 10 to 12 years: boys > 123, girls > 121; 13-17 years: boys > 136, girls > 128;  
 Supine diastolic BP: 10 to 12 years: ≥ 78; 13 to 17 years: boys ≥ 85, girls ≥ 82  
 From Sponsor Table SA14 in Summary Clin Safety document

### Height and Weight

Per request of the Division, the Sponsor provided a separate submission addressing the metabolic effects of quetiapine on adult and pediatric/adolescent patients in their clinical trials database. These data, while also summarized briefly in this review, will be more extensively evaluated in a separate review document and will also evaluate the dose-response relationship to these metabolic effects.

Of note, for Study 112, only ~5.5% of patients in the quetiapine 400 and 800 mg/day group had been taking olanzapine prior to enrollment into the study compared to 13.3% of patients in the placebo group. Therefore, changes from baseline in the quetiapine group are unlikely to include substantial numbers of patients who are having weight decreases due to discontinuation of prior olanzapine therapy.

### Mean Change Analyses

In Studies 112 and 149, quetiapine was associated with a significantly greater mean increase in weight compared to placebo.

Study 112 was an international trial. The Sponsor did provide a separate summary table for mean change in weight for the different pooled geographic locations. For the USA sites, the change from baseline to final visit was +2.7 kg (quetiapine 400 mg, n = 20), +2.0 kg (quetiapine 800 mg, n = 22) and -0.2 kg (placebo, n = 25).

Table 66. Height and Weight: Mean (SD) Change from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 75
Weight (kg)	1.9 (2.5)	1.5 (2.6)	-0.1 (2.8)
Height (cm)	0.3 (0.81)	0.3 (0.88)	0.2 (0.69)

From Sponsor Table 59 in Clinical Study Report (Study 112)

Table 67. Height and Weight: Mean (SD) Change from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg/day N = 95	Quetiapine 600 mg/day N = 98	Placebo N = 90
Weight (kg)	1.7 (2.0)	1.7 (2.3)	0.4 (1.7)
Height (cm)	0.5 (0.96)	0.5 (0.89)	0.3 (0.76)

From Sponsor Table 59 in Clinical Study Report (Study 112)

### Outlier Analyses

In Study 112, 23.2% of patients in the quetiapine 400 mg/day group, 18.2% of patients in the quetiapine 800 mg/day group and 6.8% of patients in the placebo group had a  $\geq 7\%$  weight gain at Day 42.

In Study 149, 14.5% of patients in the quetiapine 400 mg/day group, 9.9% of patients in the quetiapine 600 mg/day group and 0% patients in the placebo group had a  $\geq 7\%$  weight gain at Day 21.

The pooled analysis for Studies 112 and 149 showed 17% (57/335) of patients in the quetiapine group gained  $> 7\%$  weight compared to 2.5% (4/163) of patients in the placebo group. A pooled analysis by age cohort (Table 68) show that, in the quetiapine group, 14.1% of patients 10 - 12 years of age and 18% of patients 13 to 17 years of age gained  $> 7\%$  weight (compared to 0% and 3.1% of patients in the respective placebo age cohorts).

Table 68. Weight: Clinically Important Shifts ( $\geq 7\%$  Increase) at Any Time by Age Cohort – Pooled Analysis for Studies 112 and 149

	10 – 12 Years						13 – 17 Years					
	Quetiapine N = 85			Placebo N = 36			Quetiapine N = 255			Placebo N = 129		
	N	n	%	N	n	%	N	n	%	N	n	%
BMI Group												
< 18.5	21	5	23.8	7	0	0	44	15	34.1	14	2	14.3
18.5 - < 25	43	7	16.3	17	0	0	134	26	19.4	72	2	2.8
25 - < 30	16	0	0	9	0	0	42	3	7.1	27	0	0
30 - < 40	4	0	0	2	0	0	23	0	0	12	0	0
$\geq 40$	0	0	0	0	0	0	2	0	0	2	0	0
<b>Total</b>	<b>85</b>	<b>12</b>	<b>14.1</b>	<b>36</b>	<b>0</b>	<b>0</b>	<b>250</b>	<b>45</b>	<b>18.0</b>	<b>127</b>	<b>4</b>	<b>3.1</b>

From Sponsor Table SA15 from Summary Clin Safety document

#### 7.4.4 Electrocardiograms (ECGs)

Due to the effect of quetiapine on heart rate, the Sponsor focused primarily on the QTcF as the main correction factor for the QT interval. The reviewer agrees that this approach was appropriate.

#### Mean Change Analyses

In general, minimal effect on ECG was noted in Studies 112 and 149. Mean changes in QTcF were inconsistent between doses and studies and all < 5 msec, so not considered to be clinically relevant. The mean increase in heart rate was a consistent finding and potentially related to dose in Study 112. The quetiapine 400 mg/day dose was associated with a greater mean increase in heart rate in Study 149 compared to Study 112.

Table 69. ECG: Mean (SD) Change from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day N = 73 n = 64	Quetiapine 800 mg/day N = 74 n = 64	Placebo N = 75 n = 65
Heart rate (bpm)	3.8 (16.5)	11.2 (14.9)	-3.3 (12.0)
RR interval (msec)	-42.1 (148.3)	-101.1 (127.6)	33.2 (128.3)
PR interval (msec)	-2.0 (32.1)	2.8 (13.0)	1.1 (12.5)
QRS interval (msec)	0.3 (8.5)	-0.09 (6.1)	-0.25 (6.4)
QT interval (msec)	-4.9 (26.4)	-13.0 (28.5)	2.6 (26.5)
QTcF interval (msec)	1.4 (16.5)	3.1 (17.5)	-2.6 (18.4)
QTcB interval (msec)	5.1 (22.4)	12.2 (18.9)	-5.6 (20.9)

From Sponsor Table 59 in Clinical Study Report (Study 112)

Table 70. ECG: Mean (SD) Change from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg/day N = 95 n = 90	Quetiapine 600 mg/day N = 98 n = 87	Placebo N = 90 n = 79
Heart rate (bpm)	12.8 (12.4)	13.4 (15.5)	-1.7 (11.6)
RR interval (msec)	-121.2 (123.4)	-136.1 (165.1)	18.2 (138.0)
PR interval (msec)	0.62 (14.1)	-0.76 (13.7)	-0.23 (13.9)
QRS interval (msec)	-0.98 (6.3)	-0.32 (6.0)	1.3 (6.3)
QT interval (msec)	-19.8 (23.6)	-22.8 (24.7)	1.4 (27.6)
QTcF interval (msec)	-0.80 (15.9)	-2.4 (16.4)	-1.7 (17.6)
QTcB interval (msec)	10.2 (20.0)	9.2 (24.3)	-3.4 (19.7)

From Sponsor Table 63 in Clinical Study Report (Study 149)

#### Outlier Analyses

In Study 112, 5.2% of patients in the quetiapine 400 mg/day group and 8.5% of patients in the quetiapine 800 mg/day group had shifts to high heart rate on ECG compared to 0 patients in the placebo group. No other shifts (from low or high) were noted in PR interval, QRS interval, QT interval or QTcF interval (QTcB shift data not provided by Sponsor). The definition for potentially clinically significant findings for QTcF =  $\geq 450$  msec or increase of 15% msec of baseline.

In Study 149, 1.1% of patients in the quetiapine 400 mg/day group and 2.4% of patients in the quetiapine 600 mg/day group had shifts to high heart rate on ECG compared to 0 patients in the placebo group. No other shifts (from low or high) were noted in PR interval, QRS interval, QT interval or QTcF interval (QTcB shift data not provided by Sponsor).

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

A dose-related signal was noted for some adverse events as noted in the respective sections. A dose-dependent analysis for metabolic adverse events (hyperlipidemia, weight gain and hyperglycemia) is currently under review as the Sponsor provided these data under separate request pertaining to the original request for metabolic data issued in January 2008.

### 7.5.2 Time Dependency for Adverse Events

No analysis looking at the time dependency of adverse events, in particular tolerance to events and late onset events, is available.

### 7.5.3 Drug-Demographic Interactions

The only demographic factors that were analyzed were gender and age cohort (10 to 12 years and 13 to 17 years); the latter applicable only to Study 149.

#### Gender

Prolactin and weight changes were evaluated by gender since there are known differences between males and females on these safety parameters. No gender differences were noted for either mean change in prolactin value or shifts to potentially clinically important values in Study 112. Mean changes from baseline in prolactin concentration were higher in quetiapine-treated patients than in placebo-treated patients among males and females in Study 149 (see Section 7.4.2.1, Table 47). Shifts to clinically important high prolactin concentrations occurred at a higher incidence in the quetiapine groups than in the placebo group for both males (19.4% quetiapine 400 mg/day, 14.9% quetiapine 600 mg/day, 4.1% placebo) and females (12.5% quetiapine 400 mg/day, 8.8% quetiapine 600 mg/day, 0% placebo).

Females in both quetiapine groups in Study 112 had a greater mean change from baseline in weight and BMI (quetiapine 400 mg/day: +1.7 kg and +0.6 kg/m<sup>2</sup>; quetiapine 800 mg/day: +1.1 kg, +0.3 kg/m<sup>2</sup>) compared to females in the placebo group (0.0 kg, -0.1 kg/m<sup>2</sup>). Similarly, males in both quetiapine groups in Study 112 had a greater mean change from baseline in weight and BMI (quetiapine 400 mg/day: +2.1 kg, +0.6 kg/m<sup>2</sup>; quetiapine 800 mg/day: +1.8 kg, +0.5 kg/m<sup>2</sup>) compared to males in the placebo group (-0.2 kg, -0.1 kg/m<sup>2</sup>). For females, incidence of  $\geq 7\%$  weight gain was 25% for quetiapine 400 mg/day, 10.5% for quetiapine 800 mg/day and 6.3% for placebo. For males, the incidence of  $\geq 7\%$  weight gain was 22.2% for quetiapine 400 mg/day, 22.2% for quetiapine 800 mg/day and 7.1% for placebo. Similar findings were noted for Study 149 (not included in this review).

#### Age Cohort

##### *General comment:*

Some differences in safety signals were noted when comparing the different age cohorts of 10 - 12 years of age and 13 to 17 years of age. However, it should be noted that patients 10 - 12 years of age were only recruited in Study 149, therefore, pooled comparisons for Studies 112 and 149 versus placebo also include the confound of time on drug since Study 149 was a 3-week study compared to Study 112 which was a 6-week study. For patients 10 - 12 years of age, there are only placebo-comparator data for exposure of  $\leq 3$  weeks.

The table of common adverse events (see Section 7.4.1, Table 43) provides a listing of the most common adverse events by age cohort. The Sponsor indicated that among the 7 quetiapine-treated patients with suicidal behavior, suicidal ideation, or possibly suicidal events, 5 were in the younger age group, including all 3 patients with suicidal behavior/ideation. Among the 4 quetiapine-treated patients with syncope, 3 were in the younger age group including both patients withdrawn from the study because of syncope. A table of clinically important shifts in vital signs at any time (Section 7.4.3, Table 65) provides an analysis by age cohort. In their safety summary document, the Sponsor highlights the changes in supine and standing pulse rate by age cohort. At day 21, patients 10 - 12 years had mean increases from baseline in supine pulse (quetiapine 400 mg/day: +12.2 bpm, quetiapine 600 mg/day: +12.9 bpm) that were greater than increases in supine pulse (quetiapine 400 mg/day: +6.0 bpm, quetiapine 600 mg/day: +8.6 bpm) in the 13 to 17 year old cohort. Similar findings were noted for standing pulse rate.

#### **7.5.4 Drug-Disease Interactions**

No new data are available on drug-disease interactions.

#### **7.5.5 Drug-Drug Interactions**

No new data are available on drug-drug interactions. In Study 149, adverse events were examined by concomitant psychostimulant use. In patients using psychostimulants (15.2% of the total population), the most common adverse events were similar to those in the overall population; however, the incidence of these individual adverse events was generally higher in concomitant psychostimulant users in the quetiapine 600 mg/day group. The Sponsor indicated that no other differences in safety parameters were observed to suggest an increased risk related to use of quetiapine in patients treated concurrently with psychostimulants. The Sponsor has been asked to provide an analysis of vital sign changes in patients with and without concomitant use of psychostimulants.

### **7.6 Additional Safety Evaluations**

#### **7.6.1 Human Carcinogenicity**

No new data are available on human carcinogenicity.

#### **7.6.2 Human Reproduction and Pregnancy Data**

No new data are available on human reproduction and pregnancy data

#### **7.6.3 Pediatrics and Assessment of Effects on Growth**

See section 7.4.3 (vital signs) of review for data on weight and height mean changes and categorical weight increases for Studies 112 and 149.

For Study 150, the open-label 26-week study, the Sponsor provided a summary of patients with a shift of  $\geq 0.5$  BMI z-score from baseline at anytime, end of treatment and final visit. For patients who received placebo in Studies 112 and 149, 30% had a shift at anytime, 22% had a shift at end of treatment and 31% had a shift at

week 26. For patients who received quetiapine in Studies 112 and 149, 22% had a shift at anytime, 15% had a shift at end of treatment and 18% had a shift at week 26.

For Study 150, the Sponsor provided a summary of change from open-label baseline to final visit in weight and BMI by BMI percentile CDC category. Approximately 53% of patients were in the healthy weight category, 20% in the at risk of overweight category and 22% in the overweight category.

Table 71 (Sponsor's Table). Change from Open-Label Baseline to Final Visit by Percentile CDC Category.

BMI percentile CDC category	Bipolar I Disorder (N=205)			Schizophrenia (N=175)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
0 to <5 <sup>th</sup> percentile (underweight)									
Weight (kg)	2	4.5	4.95	8	7.6	6.19	10	7.0	5.85
BMI (kg/m <sup>2</sup> )	2	2.3	2.97	8	2.7	2.29	10	2.6	2.25
5 <sup>th</sup> to <85 <sup>th</sup> percentile (healthy weight)									
Weight (kg)	83	3.6	4.86	120	3.2	9.48	203	3.4	7.91
BMI (kg/m <sup>2</sup> )	81	1.0	1.81	120	1.0	3.53	201	1.0	2.96
85 <sup>th</sup> to <95 <sup>th</sup> percentile (at risk of overweight)									
Weight (kg)	53	4.6	5.23	23	4.3	7.90	76	4.5	6.11
BMI (kg/m <sup>2</sup> )	53	1.1	1.89	23	1.1	2.69	76	1.1	2.14
95 <sup>th</sup> percentile (overweight)									
Weight (kg)	61	4.0	5.71	24	1.5	8.76	85	3.3	6.75
BMI (kg/m <sup>2</sup> )	60	0.7	2.53	24	-0.9	7.51	84	0.2	4.55

From Sponsor Table 51 in Clinical Study Report (Study 150)

Most patients in Study 150, the open-label 26-week study, did not change Tanner stage during the study and the majority of female patients had normal menstrual cycles. Of the 373 patients with Tanner staging data, 63 patients shifted 1 point, 6 patients shifted up 2 points and 1 patient shifted up 3 points.

In Study 112 (6 week study), 3 patients shifted up one point in the quetiapine groups (n = 124) and 2 patients shifted 1 point in the placebo group (n = 66).

In Study 149 (3 week study), 5 patients shifted up one point and 1 patient shifted up 2 points in the quetiapine groups (n = 175); 1 patient shifted 1 point in the placebo group (n = 81).

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

##### Overdose

There were a total of 10 cases of overdose (defined as a dose of study medication in excess of that prescribed) identified in Studies 112, 149 and 150. The maximum overdose was 2000 mg (2 unknown amounts) and this was the only case associated with adverse events (nausea, sedation). Only 3 of these cases were deemed intentional and all 3 occurred in Study 149 (bipolar mania) (see Section 7.3.5, suicidality assessment)

##### Drug Abuse

There were no reports of patients abusing quetiapine in Studies 112, 149 or 150.

#### Withdrawal or Rebound

Studies 112, 149 and 150 were not designed to assess withdrawal or rebound. Though quetiapine was titrated to the target fixed dose in Studies 112 and 149, there was no taper strategy at the end of the study nor an adequate assessment of adverse events after drug discontinuation to assess withdrawal symptoms.

## **7.7 Additional Submissions / Safety Issues**

The Sponsor has supplied additional data requested during the review of this submission. Several requests were outstanding at the time this review was completed and these will be reviewed as an addendum to this review.

## **8 Postmarket Experience**

Seroquel was first approved for marketing in the United Kingdom on July 31, 1997. By July 31, 2007, Seroquel had been approved (for use in adults) in 88 countries for schizophrenia and in 77 countries for mania. All relevant safety issues from the periodic safety update report (PSUR) covering the reporting period of August 1, 2007 to July 31, 2008 were taken into consideration for this submission. Per the Sponsor, the PSUR did not identify any new significant safety issues bearing on the established overall safety profile of quetiapine. Of note, this reviewer is not the primary reviewer for Seroquel, and therefore did not personally review any PSUR submissions for this drug. Information on the Sponsor's literature review is included in Appendix 9.1.

## 9 Appendices

### 9.1 Literature Review and References

The Sponsor indicated that they utilize both in-house facilities as well as external providers to perform searches of the published literature. The worldwide published literature is searched for all Sponsor products with no restrictions made on product formulation or route of administration. Any report of an adverse drug reaction that is a valid case published in a local journal and identified by a marketing company is translated into English and forwarded for entry onto the Patient Safety database. In addition, a comprehensive search of published medical literature regarding quetiapine use in the pediatric population was conducted on October 9, 2007, utilizing the Sponsor's inhouse database. This search yielded 1,050 clinical article abstracts and 310 review article abstracts. All abstracts were reviewed and full-text articles requested for those deemed to be relevant and then reviewed by the Patient Safety staff (health care professionals including physicians, registered nurses and pharmacists).

The search strings for pediatric patients included the following terms: infant%, neonat%, child, children, pediatric%, fetal, fetus, foet%, adolescent, juvenile%.

The findings of the literature review were consistent with the known safety of Seroquel in adults and the safety profile discussed in the proposed labeling and clinical summary of safety in the supplements.

### 9.2 Requests for Information from Sponsor

1. For Studies 112 and 149, please combine the somnolence and sedation adverse events into one term "somnolence" and recalculate the frequencies for this combined adverse event.
2. In one of the lists of principal investigators tables, there are 6 sites in Germany that participated in study 112 (sites 380, 381, 382, 383, 384, 386). However, only one site (386) enrolled 1 subject in study 112. Was there difficulty in recruiting subjects for this trial in Germany, or is there another reason for the lack of enrollment?
3. Please provide some rationale for the increases in blood pressure (systolic and diastolic) observed in the child/adolescent populations in studies 112 and 149 - this is in contrast to the orthostatic signal present in the adult population.
4. In the recent CBE submission, data for increases in blood pressure were summarized for the bipolar and schizophrenia studies in children and adolescents. It appears that these data were pooled across all doses and studies 112 and 149. Please provide a table similar to Table 64 of the clinical study report for study 149 for these data and clarify whether the systolic and diastolic blood pressure changes in labeling refer to supine or standing measurements. Were the data in labeling based on the type of data presented in Table 64? Please provide these data by age group as well (10 - 12, 13-17 yrs.) for study 149.
5. Please provide more details regarding the following serious adverse events and adverse events leading to discontinuation:

Study 149: Patient (b) (6) - Tachycardia, Blood Pressure Increased

The narrative indicates that the patient experienced these adverse events on Day 5 - however, the vital signs listing does not provide vitals obtained on Day 5. Please provide these data and any other additional vital sign readings obtained for this patient.

Study 150: Patient (b) (6) - Pulmonary Hypertension

The narrative indicates that the patient was referred to a pediatric cardiologist. Please provide the consult and pertinent follow-up for this adverse event. Did the event resolve spontaneously after quetiapine was discontinued, did the patient receive any medical treatment for the condition?

Study 150: Patient (b) (6) - Hypertensive Crisis

It appears that this patient had high blood pressure during the trial (narrative indicates from day 32 - 212) and enalapril is noted as a concomitant medication. Was enalapril initiated during the trial for high blood pressure? Listing 12.2.9.1 does not indicate high blood pressures for the visits included in the listing and the hypertensive crisis value (150/95) is not included in the listing. Please provide all blood pressures obtained for this patient. Did the patient receive any additional treatment for the 150/95 reading?

Please provide more clinical details regarding the hemorrhagic rash experienced by this patient.

Study 150: Patient (b) (6) - Suicide attempt

Please provide details regarding the suicide attempt - there is no information provided in the narrative.

It is noted that this patient also experienced neutropenia with an ANC = 0.46 on Day 85. WBCs were obtained on Days 89 and 96 but, remarkably, no ANC values were obtained for these days. The next available ANC is at Day 169 (resolution). If the value of 0.46 is correct, why was this patient not discontinued? Please comment.

Study 150: Patient (b) (6) - Syncope

The narrative notes that the patient also experienced the non-serious event "fall (mild intensity and considered related to study medication) Day 1 Day 20". Does this mean that the patient experienced falls from Day 1 to Day 20? Please clarify and provide additional information.

6. Please clarify the absolute neutrophil counts that are sporadically listed in Listing 12.2.8.2.2 (Study 150). On page 919, patient (b) (6) had a WBC count of 5.9 with 25% neutrophils which should be an ANC of 1.47. However, it appears that the ANC listed in the appropriate column indicates a value of 0.18. Please clarify.
7. Please provide a table similar to SA14 (summary-clin-safety) for standing vital sign shifts.
8. For Study 149, the inclusion criteria indicate that patients with rapid cycling bipolar disorder could be enrolled. How many patients with rapid cycling bipolar disorder were enrolled? If sufficient numbers were randomized, please perform a separate efficacy analysis for patients with and without rapid cycling bipolar disorder.
9. What % of patients received BID and TID dosing in studies 112 and 149? Was any analysis performed regarding overall tolerability (AE incidence, etc.) between these two dosing regimens?
10. For Study 150, please provide a table similar to Table 62 (patients with potentially clinically important high shifts in prolactin) in the clinical study report for Study 149. For this table, please include prolactin concentrations in ng/ml units; table 11.3.7.3.11.2 in the clinical study report for Study 150 provides the prolactin concentrations in mIU/L units.
11. In the clinical study report for Study 150, Table 11.3.8.1.14 includes the categorical shifts in eye examinations from OL baseline. Please provide more detailed information for these cases. Please provide clinical details describing the cases that shifted from normal to abnormal. Please also provide clinical details describing the cases that were categorized as abnormal at OL baseline and that remained abnormal (e.g. were the same/similar abnormalities noted).

12. For Study 149, please provide an analysis of mean change in vital signs from baseline to final visit (supine and standing pulse, systolic BP and diastolic BP) for patients on concurrent psychostimulants and those not on concurrent psychostimulants. Please also provide an analysis of clinically important shifts at any time in vital signs for these same groups of patients. For patients with the clinically important shifts at anytime, please provide a line listing of all vital signs.
13. In the clinical study report for Study 150, Table 11.3.8.1.14 includes the categorical shifts in eye examinations from OL baseline. Please provide more detailed information for these cases. Please provide clinical details describing the cases that shifted from normal to abnormal. Please also provide clinical details describing the cases that were categorized as abnormal at OL baseline and that remained abnormal (e.g. were the same/similar abnormalities noted).
14. For Study 149, please provide an analysis of mean change in vital signs from baseline to final visit (supine and standing pulse, systolic BP and diastolic BP) for patients on concurrent psychostimulants and those not on concurrent psychostimulants. Please also provide an analysis of clinically important shifts at any time in vital signs for these same groups of patients. For patients with the clinically important shifts at anytime, please provide a line listing of all vital signs.
15. For Studies 112 and 149, please provide the subject identifiers for subjects with shifts to high in vital sign parameters (pulse, blood pressure) and provide listings for all study vital sign readings (including unscheduled visits) for these subjects including vital signs obtained in Study 150 for those subjects who continued in the open-label extension study. Did any subjects require treatment with antihypertensive medications?
16. Please provide mean change in prolactin concentration for studies 112 and 149 only for the subset of patients with normal prolactin at baseline.

### 9.3 Inclusion and Exclusion Criteria for Study 112

#### Inclusion Criteria

1. Provision of written informed consent by one or both parents or by legal guardian prior to any study procedure.
2. Provision of written assent by the patient prior to any study procedure.
3. Male or female, aged 13 to 17 years at randomization, hospitalized or outpatient.
4. If female and of childbearing potential, must have used a reliable method of contraception. Reliable methods included abstinence, hormonal contraceptives (e.g. oral contraceptive or long-term injectable or implantable hormonal contraceptive), double-barrier methods (e.g. condom and diaphragm, condom and foam, condom and sponge), intrauterine devices, and tubal ligation.
5. All female patients needed to have the absence of pregnancy confirmed by a negative  $\beta$ -human chorionic gonadotropin before randomization.
6. DSM-IV criteria for schizophrenia confirmed by the K-SADS-PL.
7. The Social Communication Questionnaire (SCQ) was administered to assess for pervasive developmental disorders. Patients with an SCQ score of  $\geq 15$  and who otherwise met entrance criteria must have had a documented history of delusions or hallucinations.
8. Patients with a secondary diagnosis of depression may have continued treatment with an antidepressant if clinically advised by the investigator, providing the antidepressant was permitted and the dose was stable for  $\geq 30$  days preceding randomization.
9. PANSS score  $> 60$  and a score of  $\geq 4$  on at least one of the following items: delusions, conceptual disorganization or hallucinations at both screening and randomization.
10. Willingness to agree not to harm self

11. Had a parent or legal guardian accompany the patient at each scheduled study visit, provided reliable information, and was responsible for receiving and dispensing study medication.
12. Willingness to adhere to the schedule of assessments.

Exclusion Criteria

1. Secondary DSM-IV Axis I diagnoses of Bipolar Disorders including Cyclothymia, Schizophreniform Disorder, Schizoaffective Disorder, Psychotic Disorder Not Otherwise Specified, and acute (< 3 months) Post-traumatic Stress Disorder.
2. Premorbid IQ < 70 or diagnosis of mental retardation.
3. Psychosis judged to be the direct physiological consequence of a medical condition or treatment. These conditions included degenerative neurological conditions (e.g. Parkinson's disease, Huntington's disease), cerebrovascular disease (e.g. stroke), metabolic conditions (e.g. vitamin B12 deficiency), autoimmune conditions (e.g. systemic lupus erythematosus), viral or other infections (e.g. hepatitis, mononucleosis, HIV), and cancers.
4. Psychosis judged to be the direct physiological effect (e.g. intoxication, withdrawal) of an abused medication or substance.
5. History of any serious suicide attempt that required medical intervention or current suicidal risk that could not be safety managed as determined by the clinical judgment of the investigator.
6. Serious homicidal risk or homicidal behaviors within the past 3 months that resulted in adjudication.
7. Known intolerance for or lack of response to quetiapine, as judged by the investigator.
8. Contraindications as detailed in country-specific prescribing information for quetiapine.
9. For female patients, pregnancy or lactation.
10. Substance abuse or dependence including alcohol (except for caffeine or nicotine dependence) as defined in DSM-IV, within 1 month prior to screening.
11. Inability to discontinue psychoactive medications prior to randomization.
12. Use of haloperidol decanoate, fluphenazine decanoate, or risperidone microspheres
13. ECT within 30 days prior to screening.
14. Use of potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, saquinavir) in the 14 days preceding randomization.
15. Use of potent CYP3A4 inducers (e.g. phenytoin, carbamazepine, barbiturates, rifampin, glucocorticoids, Saint John's Wort) in the 14 days preceding randomization.
16. TSH hormone concentration more than 10% above the upper limit of the normal range.
17. Laboratory test results outside the reference range and considered by the investigator to be clinically significant.
18. Baseline QTcF  $\geq$  450 ms at baseline.
19. Renal, cardiovascular, hepatic, hematologic, endocrinologic, ophthalmologic, or other disease or clinical finding that was unstable or that in the opinion of the investigator would be negatively affected by study medication or that would affect study medication.
20. Unstable diabetes mellitus with a baseline HbA1c  $\geq$  8.5.
21. Patients admitted to a hospital for treatment of diabetes or diabetes-related illness in past 12 weeks.
22. Not under the care of a physician responsible for the patient's diabetes care.
23. Diabetes mellitus clinically unstable in the opinion of the physician responsible for the patient's diabetes management at the time of baseline.
24. The physician responsible for the patient's diabetes care had not approved the patient's participation in the study.
25. The patient had not been on the same dose of the oral hypoglycemic drug(s) and/or diet for the 4 weeks prior to randomization. For thiazolidinediones (glitazones) this period should not have been less than 8 weeks.
26. A patient taking insulin whose daily dose on one occasion in the past 4 weeks was more than 10% above or below their mean dose in the preceding 4 weeks.

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27. If the patient's CBC with WBC differential showed an ANC < 1.0 x 10<sup>9</sup>/L, the test was repeated within 24 hours. If the value remained < 1.0 x 10<sup>9</sup>/L, the patient was excluded.
28. Medical condition that would affect the absorption, distribution, metabolism, or excretion of study medication.
29. History of seizure disorder, except febrile convulsions.
30. Use of experimental drug within 30 days of randomization.
31. Previous participation in this study.
32. Significant medical illness which could prevent patient from completing double-blind treatment.

9.4 Study Assessments Flow Chart – Study 112

Study plan	Screening	Washout period	Randomization <sup>a</sup>	Double-blind treatment					
				3	4	5	6	7	8 <sup>b</sup> /Final
Visit <sup>b</sup>	1	Up to 28 days	2	3	4	5	6	7	8 <sup>b</sup> /Final
Day	Screening		1	7	14	21	28	35	42
Informed consent, assent, demography, history	√								
Inclusion/exclusion criteria	√		√						
Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL) and Social Communication Questionnaire (SCQ)	√								
Urine drug screen and urinalysis	√								√
Physical examination <sup>c</sup>	√								√
Tanner staging <sup>c</sup>	√								√
Vital signs <sup>d</sup> , height, weight, temperature	√*		√	√	√	√	√	√	√
12-lead electrocardiogram	√*								√
Laboratory tests to include all of the following: Clinical chemistry <sup>e</sup> including lipid panel Insulin level and HbA1c Thyroid function and prolactin concentration β-hCG <sup>f</sup>	√*						√*		√
Hematology <sup>g, h</sup>	√						√		√
Genetic sampling <sup>h</sup>	√								
Positive and Negative Syndrome Scale (PANSS)	√		√	√	√	√	√	√	√
Clinical Global Impression (CGI) Severity of Illness and Global Improvement items <sup>g</sup>			√	√	√	√	√	√	√
Children's Global Assessment Scale (CGAS)			√						√
Caregiver Strain Questionnaire <sup>g</sup> (CGSQ)			√						√

Study plan	Screening	Washout period	Randomization <sup>a</sup>	Double-blind treatment					
				3	4	5	6	7	8 <sup>b</sup> /Final
Visit <sup>b</sup>	1	Up to 28 days	2	3	4	5	6	7	8 <sup>b</sup> /Final
Day	Screening		1	7	14	21	28	35	42
Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS)			√	√	√	√	√	√	√
Children's Depression Rating Scale – Revised (CDRS-R) <sup>f</sup>			√	√	√	√	√	√	√
Adverse event recording	√		√	√	√	√	√	√	√
Prior and concomitant medication recording	√		√	√	√	√	√	√	√
Study drug dispensing			√*	√	√	√	√	√	
Drug accountability and treatment compliance				√	√	√	√	√	√

Clinical Review  
Cara Alfaro, Pharm.D.  
NDA 20-639 SE5-045 & SE5-046  
Seroquel (quetiapine fumarate)

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- <sup>a</sup> Study drug was titrated up starting at Day 1 (see Table 5).
- <sup>b</sup> Visit window:  $\pm 3$  days of scheduled visit date.
- <sup>c</sup> End of double-blind treatment.
- <sup>d</sup> Physical exam included routine ophthalmologic assessment at Screening and on Day 42 or final visit.
- <sup>e</sup> Was completed by a physician or designated medical staff. A self-report or family-report assessment was not allowed.
- <sup>f</sup> Blood pressure and pulse rate were obtained in supine and standing positions.
- <sup>g</sup> Assessment was repeated if washout period was  $\geq 14$  days.
- <sup>h</sup> Only fasting plasma glucose was obtained. Other clinical chemistry, insulin level, HbA<sub>1c</sub>, thyroid function and prolactin concentration, and  $\beta$ -hCG were not required at this visit.
- <sup>i</sup> Blood samples collected for clinical chemistry were obtained under fasting conditions. Fasting was defined as not having ingested food or liquids other than water for  $\geq 8$  hours. Fasting blood sample was drawn between 8:00 AM and 10:00 AM.
- <sup>j</sup> For female patients only at Visits 1 and 8. Could be completed at additional visits if clinically indicated.
- <sup>k</sup> If the patient presented with a fever, pharyngitis, or other signs and symptoms of infection at any time, a CBC with differential was completed.
- <sup>l</sup> If the patient's CBC with WBC differential showed an ANC  $< 1.0 \times 10^9/L$ , the test was repeated within 24 hours. If it remained  $< 1.0 \times 10^9/L$ , the patient was discontinued.
- <sup>m</sup> Genetic sampling was optional for both sites and patients at any time during the study.
- <sup>n</sup> The CGI Global Improvement item, which assessed changes from baseline, was not recorded at randomization.
- <sup>o</sup> Was completed by parent or legal guardian during the visit.
- <sup>p</sup> New patients started at Visit 2, ongoing patients started at the next scheduled visit. Did not go back and complete prior visits.
- <sup>q</sup> The first dose of study medication was taken on the evening of Day 1, which must have occurred no more than 14 days after baseline safety assessments were obtained.

## 9.5 Inclusion and Exclusion Criteria for Study 149

### Inclusion Criteria

1. Provision of written informed consent by one of both parents or by legal guardian prior to any study procedure.
2. Provision of written assent by the patient prior to any study procedure.
3. Male or female, aged 10 to 17 years at randomization, hospitalized or outpatient
4. If female and of childbearing potential, must have used a reliable method of contraception. Reliable methods included abstinence, hormonal contraceptives (e.g. oral contraceptive or long-term injectable or implantable hormonal contraceptive), double-barrier methods (e.g. condom and diaphragm, condom and foam, condom and sponge), intrauterine devices, and tubal ligation.
5. All female patients needed to have the absence of pregnancy confirmed by a negative serum  $\beta$ -hCG) before randomization
6. DSM-IV criteria for Bipolar I mania confirmed by the K-SADS-PL. Patients with rapid cycling or who experienced a first manic episode were included. Patients could also have had a secondary diagnosis of ADHD. Patients with ADHD could, if judged necessary by the investigator, have continued the psychostimulant treatment if the prescribed dose had been stable for  $\geq 30$  days preceding randomization.
7. Willingness to agree not to harm self.
8. YMRS score  $\geq 20$  at both screening and randomization.
9. Had a parent or legal guardian accompany the patient at each scheduled study visit, provided reliable information, and was responsible for receiving and dispensing study medication.
10. Willingness to adhere to the schedule of assessments.

### Exclusion

1. Diagnosis of a current DSM-IV Axis I disorder with the exception of those noted in the inclusion criteria. Excluded diagnoses included Tourette's disorder, OCD, acute ( $< 3$  months) PTSD, panic disorder, pervasive developmental disorders.
2. Premorbid IQ  $< 70$  or diagnosis of mental retardation.
3. Psychosis judged to be the direct physiological consequence of a medical condition or treatment. These conditions include degenerative neurological conditions (e.g. Parkinson's disease, Huntington's disease), cerebrovascular disease (e.g. stroke), metabolic conditions (e.g. vitamin B12 deficiency), autoimmune conditions (e.g. SLE), viral or other infections (e.g. hepatitis, mononucleosis, HIV), and cancers.
4. Psychosis judged to be the direct physiological effect of an abused medication or substance (e.g. intoxication, withdrawal).
5. Current manic episode judged to be the direct physiological effect of psychostimulant or antidepressant medication.

6. History of any serious suicide attempt that required medical intervention or current suicidal risk that cannot be safely managed as determined by the clinical judgment of the investigator.
7. Serious homicidal risk or homicidal behaviors within the past 3 months that resulted in adjudication
8. Known intolerance for or lack of response to quetiapine, as judged by the investigator
9. For female patients, pregnancy or lactation
10. Substance abuse or dependence including alcohol (except for caffeine or nicotine dependence), as defined in DSM-IV, within 1 month prior to screening.
11. Inability to discontinue psychoactive medications prior to randomization
12. Use of haloperidol decanoate, fluphenazine decanoate or risperidone microspheres within 1 dosing interval prior to randomization
13. ECT within 30 days prior to screening
14. Use of potent CYP3A4 inhibitors in the 14 days preceding randomization
15. Use of potent CYP3A4 inducers in the 14 days preceding randomization
16. TSH hormone concentration > 10% above the upper limit of normal range
17. Laboratory test results outside the reference range and considered by the investigator to be clinically significant
18. Baseline QTcF interval > 450 msec at baseline
19. Renal, cardiovascular, hepatic, hematologic, endocrinologic, ophthalmologic, or other disease or clinical finding that was unstable or that in the opinion of the investigator would be negatively affected by study medication or that would affect study medication
20. Unstable diabetes mellitus with a baseline HbA1c  $\geq$  8.5.
21. Patients admitted to a hospital for treatment of diabetes or diabetes related illness in past 12 weeks.
22. Not under the care of a physician responsible for the patient's diabetes care.
23. Diabetes clinically unstable in the opinion of the physician responsible for the patient's participation in the study.
24. The patient had not been on the same dose of oral hypoglycemic drug(s) and/or diet for the 4 weeks prior to randomization. For thiazolidinediones (glitazones) this period should not have been less than 8 weeks.
25. A patient taking insulin whose daily dose on one occasion in the past 4 weeks was more than 10% above or below their mean dose in the preceding 4 weeks.
26. If the patient's CBC and WBC differential showed an ANC  $< 1.0 \times 10^9/L$ , the test was repeated within 24 hours. If the value remained  $< 1.0 \times 10^9/L$ , the patient was excluded.
27. Medical condition that would affect absorption, distribution, metabolism, or excretion of study medication
28. History of seizure disorder, except febrile convulsions
29. Use of experimental drug within 30 days of randomization
30. Previous participation in this study
31. Significant medical illness which could prevent patient from completing double-blind treatment
32. Patients with asthma treated with oral steroids within 3 months prior to randomization
33. Concurrent cognitive-behavior therapy initiated within 6 weeks prior to randomization

### 9.6 Study Assessments Flow Chart for Study 149

Study plan	Screening	Washout period Up to 28 days	Randomization <sup>b</sup>	Double-blind treatment			
	1		2	3	4	5	6 <sup>c</sup> /Final
Day	Screening		1	4	7	14	21
<b>General events/assessments</b>							
Informed consent, assent, and demography, history	√						
Inclusion/exclusion criteria	√		√				
Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL)	√						
Physical examination <sup>d</sup>	√						√
Tanner Staging	√						√
Vital signs <sup>e</sup> , height, weight, temperature	√ <sup>a</sup>		√	√	√	√	√
12-lead electrocardiogram	√ <sup>a</sup>						√
Laboratory tests to include all of the following: Clinical chemistry <sup>f</sup> including lipid panel HbA1c Thyroid function and prolactin concentration Hematology <sup>g</sup> β-human chorionic gonadotropin (β hCG) <sup>i</sup>	√ <sup>a</sup>						√
Genetic Sampling <sup>j</sup>	√						
Urine drug screen and urinalysis	√						√
Young Mania Rating Scale (YMRS)	√		√	√	√	√	√
Clinical Global Impression – Bipolar (CGI-BP) Severity of Illness and Global Improvement items <sup>k</sup>			√	√	√	√	√
Children’s Depression Rating Scale – Revised (CDRS-R)			√	√	√	√	√
Overt Aggression Scale – Modified (OAS-M)			√	√	√	√	√
Children’s Global Assessment Scale (CGAS)			√				√

Study plan	Screening	Washout period Up to 28 days	Randomization <sup>b</sup>	Double-blind treatment			
	1		2	3	4	5	6 <sup>c</sup> /Final
Day	Screening		1	4	7	14	21
Caregiver Strain Questionnaire (CGSQ) <sup>l</sup>			√				√
Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS)			√		√	√	√
Adverse event recording	√		√	√	√	√	√
Prior and concomitant medication recording	√		√	√	√	√	√
Study drug dispensing			√ <sup>m</sup>	√	√	√	
Drug accountability and treatment compliance				√	√	√	√

<sup>a</sup> Visit window: ± 3 days of scheduled visit date.  
<sup>b</sup> Study drug was titrated up starting at Day 1 (see Table 5).  
<sup>c</sup> End of double-blind treatment.  
<sup>d</sup> Physical exam included routine ophthalmologic assessment at Screening and on Day 21 or final visit.  
<sup>e</sup> Assessment was repeated only if washout period is ≥14 days.  
<sup>f</sup> Blood pressure and pulse rate were obtained in supine and standing positions.  
<sup>g</sup> Blood samples collected for clinical chemistry were obtained under fasting conditions. Fasting was defined as not having ingested food or liquids other than water for ≥8 hours. Fasting blood sample was drawn between 8:00 AM and 10:00 AM.  
<sup>h</sup> If the patient presented with a fever, pharyngitis, or other signs and symptoms of infection at any time, a CBC with differential was completed.  
<sup>i</sup> For female patients only and was completed at any visit based on discussion with the patient.  
<sup>j</sup> Genetic sampling was optional for both sites and patients at any time during the study.  
<sup>k</sup> The CGI-BP Global Improvement item which assessed change from baseline was not recorded at randomization.  
<sup>l</sup> Was completed by parent and legal guardian during visit.  
<sup>m</sup> The first dose of study medication was taken on the evening of Day 1, which must have occurred no more than 10 days after baseline safety assessments were obtained.

9.7 Potentially Clinically Important Definitions for Hematology, Chemistry and ECG Values

	Low	High
Hematocrit	≤ 0.35	
Hemoglobin (g/dL)	≤ 11.5	≥ 17.2 g/dL
RBC (cells/L)	≤ 3x10 <sup>12</sup>	≥ 6x10 <sup>12</sup>
Platelet count (cells/L)	≤ 100x10 <sup>9</sup>	≥ 600x10 <sup>9</sup>
WBC		
Neutrophils	≤ 15%	
Absolute (calculated) (cells/L)	≤ 1.5x10 <sup>9</sup>	≥ 10x10 <sup>9</sup>
Eosinophils	≥ 10%	
Absolute (calculated) (cells/L)	≥ 1x10 <sup>9</sup>	
Basophils	≥ 0.5x10 <sup>9</sup>	
Lymphocytes	≤ 0.5x10 <sup>9</sup>	> 6x10 <sup>9</sup>
Monocytes	≥ 1.4x10 <sup>9</sup>	
Chemistry		
ALT		≥ 3xULN
AST		≥ 3xULN
Alkaline phosphatase		≥ 3xULN
Total bilirubin		≥ 1.5xULN
HbA1c (%)		> 7.5%
Sodium (mmol/L)	≤ 132	≥ 152
Glucose (mg/dL)		
Fasting	≤ 45	≥ 126
Random	≤ 45	≥ 200
BUN (mg/dL)		≥ 21
Creatinine (mg/dL)		≥ 1.357
Potassium (mmol/L)	≤ 3.0	≥ 5.5
Chloride (mmol/L)	≤ 90	≥ 120
CO2 (mmol/L)	≤ 18	≥ 30
Total cholesterol (mg/dL)		≥ 240
HDL (mg/dL)	≤ 40	
LDL (mg/dL)		≥ 160
Triglycerides (mg/dL)		≥ 200
Total T4 and Free T4	≤ 0.8xLLN	≥ 1.2xULN
TSH (mIU/L)		> 5
Prolactin (ng/ml)		> 26 (females) > 20 (males)

ECG Parameter	Criterion Value	Change from Baseline
Heart rate (bpm)	> 110, < 50	Increase ≥ 15, decrease ≥ 15
PR (msec)	≥ 200	
QRS (msec)	≤ 50, ≥ 100	
QT (msec)	≥ 500, ≤ 200	Increase ≥ 60 msec
QTcF (msec)	≥ 450	Increase 15% msec of baseline

9.8 Potentially Clinically Significant Low ANC

Study	Treatment	Gender/Age	Baseline ANC (10 <sup>9</sup> /L)	Lowest Value/Day	Final Visit	Comments
112	QTP 400	M, 15	2.3	1.46 (Day 46)	1.46 (Day 46)	Discontinued
		M, 14	4.22	1.44 (Day 31)	2.20 (Day 45)	
		M, 16	1.30	1.19 (Day 38)		
		F, 17	1.61	0.99 (Day 30)	1.01 (Day 43)	
		F, 17	4.45	1.52 (Day 34)	2.25 (Day 33)	
	QTP 800	M, 13	1.73	1.14 (Day 33)	1.15 (Day 41)	
		M, 15	1.62	1.35 (Day 28)	2.40 (Day 46)	
	Placebo	M, 13	3.39	1.29 (Day 30)	1.33 (Day 43)	
		M, 13	1.99	1.41 (Day 27)	1.64 (Day 41)	
		M, 17	2.25	1.04 (Day 41)	1.04 (Day 41)	
M, 14		NA	1.28 (Day 28)	0.75 (Day 48)		
M, 14		1.44	1.63 (Day 31)	1.3 (Day 43)		
F, 16		1.28	-	-		
149	QTP 400	F, 12	1.8		1.4 (Day 19)	1.4 (Day -2)
		M, 14	3.7		1.4 (Day 19)	
		F, 13	2.3		1.5 (Day 22)	
		F, 12	3.3	1.5 (Day 11)	2.7 (Day 14)	
		M, 10	2.4	1.2 (Day 20)	2.8 (Day 29)	
		M, 13	1.5		1.3 (Day 19)	
	QTP 600	M, 12	2.8		1.5 (Day 22)	1.6 (Day -7)
		M, 12	2.4		1.5 (Day 19)	
		F, 12	2.1		1.5 (Day 20)	
		M, 13	2.5		1.1 (Day 24)	
		M, 14	1.3		1.3 (Day 20)	
	Placebo	M, 12	1.6		1.0 (Day 23)	1.5 (Day -4)
		M, 13	1.7	1.2 (Day 22)	3.0 (Day 33)	

### 9.9 Mean Orthostatic Changes in Pulse and Blood Pressure

Mean Orthostatic Changes in Pulse and Blood Pressure – Study 112

		Quetiapine 400 N = 73		Quetiapine 800 N = 74		Placebo N = 75	
		n	Mean	n	Mean	n	Mean
Pulse (bpm)	Screen	73	7.4	71	7.8	74	7.1
	Day 1	70	6.7	71	6.2	73	5.7
	Day 7	73	9.3	72	7.3	72	7.3
	Day 14	70	7.5	70	6.3	72	4.8
	Day 21	67	8.4	67	5.3	65	4.8
	Day 28	61	6.6	64	5.9	57	5.6
	Day 35	58	9.1	62	5.6	51	5.5
	Day 42	55	6.4	55	3.9	44	4.4
	Final	73	6.8	74	4.7	73	4.9
Systolic BP (mmHg)	Screen	73	0.4	71	-0.4	74	-0.6
	Day 1	70	-1.3	71	0.7	73	-1.3
	Day 7	73	-1.7	72	-1.4	72	-2.0
	Day 14	70	-3.0	70	-0.5	72	-1.1
	Day 21	67	-1.5	67	-1.6	65	-0.6
	Day 28	61	-0.7	63	-1.0	57	-1.7
	Day 35	58	-0.1	62	-0.4	51	0.2
	Day 42	55	-1.1	55	-1.2	44	-0.6
	Final	73	-0.9	74	-0.4	73	-1.1
Diastolic BP (mmHg)	Screen	73	2.1	71	2.6	74	3.3
	Day 1	70	2.1	71	1.9	73	3.3
	Day 7	73	2.3	72	1.9	72	2.2
	Day 14	70	1.9	70	2.7	72	4.0
	Day 21	67	2.1	67	2.9	65	2.2
	Day 28	61	3.5	63	1.8	57	3.4
	Day 35	58	3.4	62	1.9	51	2.0
	Day 42	55	3.4	55	2.4	44	1.6
	Final	73	2.8	74	2.8	73	2.1

From Sponsor Table 11.3.8.2.3.1, 11.3.8.2.3.2, 11.3.8.2.3.3 in Clinical Study Report (Study 112)

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Mean Orthostatic Changes in Pulse and Blood Pressure – Study 149

		Quetiapine 400 N = 95		Quetiapine 600 N = 98		Placebo N = 90	
		n	Mean	n	Mean	n	Mean
Pulse (bpm)	Screen	93	9.4	98	8.8	89	8.8
	Day 1	88	8.3	93	8.1	87	8.4
	Day 4	80	9.7	73	10.3	64	9.8
	Day 7	88	8.9	90	10.2	85	9.0
	Day 14	78	8.5	82	7.7	73	9.7
	Day 21	76	9.5	81	9.2	68	10.1
Systolic BP (mmHg)	Screen	93	-1.1	98	-1.4	89	-0.7
	Day 1	88	-0.3	93	0.3	87	-1.6
	Day 4	79	-0.7	72	-3.3	64	-0.8
	Day 7	88	-1.3	90	-1.7	85	0.1
	Day 14	78	-0.1	82	-1.1	73	0.6
	Day 21	76	0.2	81	-1.3	68	0.6
Diastolic BP (mmHg)	Screen	93	3.3	98	2.5	89	2.8
	Day 1	88	3.3	93	3.2	87	3.8
	Day 4	79	4.0	72	0.6	64	3.9
	Day 7	88	3.4	90	1.0	85	5.0
	Day 14	78	2.7	82	1.7	73	3.4
	Day 21	76	3.9	81	2.1	68	3.4

From Sponsor Table 11.3.8.2.3.1, 11.3.8.2.3.2, 11.3.8.2.3.3 in Clinical Study Report (Study 149)

9.10 Study Assessments Flow Chart – Study 150

Study plan	Open-label baseline		Open-label treatment								
	1 Baseline/Screen End of DB study <sup>b</sup>		2	3	4	5	6	7	8	9	10 <sup>d</sup> /Final
Day	0	1 <sup>a</sup>	7	14	21	28					
Week	1-7 days after end of DB study <sup>c</sup>		1	2	3	4	8	12	16	20	26
Informed consent and assent	√										
Inclusion/exclusion criteria	√										
Physical examination <sup>e</sup>	√										√
Ophthalmological slit-lamp examination <sup>f</sup>	√										√
Tanner staging <sup>g</sup>	√										√
Vital signs <sup>h</sup> /height/weight/oral temperature	√		√	√	√	√	√	√	√	√	√
12-lead electrocardiogram	√							√ <sup>h</sup>			√
Laboratory tests to include all of the following: Clinical chemistry <sup>i</sup> including lipid panel Insulin level and HbA1c Thyroid function and prolactin concentration β-hCG <sup>j</sup>	√							√			√
Hematology <sup>k,l</sup>	√					√	√	√			√
Urine drug screen and urinalysis	√										√
Young Mania Rating Scale (YMRS) <sup>m</sup>	√					√	√		√		√
Clinical Global Impression-Bipolar (CGI-BP) Severity of Illness and Global Improvement items <sup>n</sup>	√		√	√	√	√	√	√	√	√	√
Positive and Negative Syndrome Scale (PANSS) <sup>o</sup>	√					√	√		√		√

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 Seroquel (quetiapine fumarate)

Clinical Global Impression (CGI) Severity of Illness and Global Improvement items <sup>a</sup>	√		√	√	√	√	√	√	√	√	√	√
Clinical Global Assessment Scale (CGAS)	√											√
Caregiver Strain Questionnaire (CGSQ) <sup>a</sup>	√											√
Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS)	√		√	√	√	√	√	√	√	√	√	√
Children's Depression Rating Scale – Revised (CDRS-R) <sup>a</sup>	√		√	√	√	√	√	√	√	√	√	√
Adverse events recording	√		√	√	√	√	√	√	√	√	√	√
Prior and concomitant medication recording	√		√	√	√	√	√	√	√	√	√	√
Study drug dispensing		√ <sup>b</sup>	√	√	√	√	√	√	√	√	√	
Drug accountability and treatment compliance			√	√	√	√	√	√	√	√	√	√

- <sup>a</sup> Visit window: ± 3 days of scheduled visit date for Visits 1 to 4, ± 7 days for Visits 5 to 10 (early withdrawal).
- <sup>b</sup> End-of-study assessments from Study 149 or Study 112 were carried forward as baseline assessments for OL study.
- <sup>c</sup> Baseline/Screening visit was to be completed no more than 7 days from the end of the preceding double-blind study (Study 149 or Study 112).
- <sup>d</sup> End of OL treatment. Please note that there is a 6-week period between Visits 9 and 10.
- <sup>e</sup> Physical examination included routine ophthalmologic assessment.
- <sup>f</sup> Ophthalmologic slit-lamp examination was to be completed within 14 days from baseline visit and no greater than 14 days after end of study treatment. This was completed by an ophthalmologist.
- <sup>g</sup> Blood pressure was obtained in the supine and standing positions.
- <sup>h</sup> An ECG resulting in a QTc (Fridericia) ≥450 milliseconds was to be repeated. If QTc (Fridericia) remained ≥450 milliseconds the pediatric cardiologist was to be consulted regarding continuation in study.
- <sup>i</sup> Blood samples collected for clinical chemistry were to be obtained under fasting conditions. Fasting was defined as not having ingested food or liquids other than water for ≥8 hours. Fasting blood samples were to be drawn between 8:00 – 10:00 AM.

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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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Cara Alfaro  
5/11/2009 10:43:25 AM  
PHARMACIST

Ni Aye Khin  
5/11/2009 12:58:38 PM  
MEDICAL OFFICER

This set of NDA supplements will be presented at  
the PDAC meeting scheduled for 6/9/09 and 6/10/09;  
a memo to file to be followed after  
discussion at the PDAC meeting.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

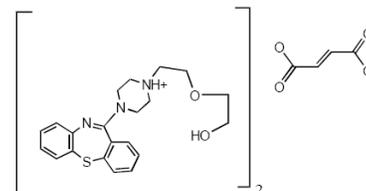
**020639Orig1s046**

**CHEMISTRY REVIEW(S)**

**Division of Post Approval Marketing Evaluation IV  
Chemist Review of Supplement**

1. Division of Post Approval Marketing IV
2. NDA Number: N20639 SE1-045 and 046
3. Supplement Numbers/Dates:  
Letter Date: October 28, 2008  
Stamp Date: October 28, 2008
4. Amendments/Reports/Dates:
5. Received by Chemist: April 16, 2009
6. Applicant Name and Address: Astra Zeneca Pharmaceuticals LP  
1800 Concord Pike  
PO Box 8355  
Wilmington, DE 19803-8355
7. Name of the Drug: Seroquel® Tablets
8. Nonproprietary name: Quetiapine Tablets
9. Chemical Structure/ Chemical Name:
10. Dosage Form: Tablets
11. Potency: 300 mg
12. Pharmacological Category: schizophrenia and other psychotic disorders
13. How Dispensed: XXX(RX) \_\_\_\_\_(OTC)
14. Related IND/NDA/DMF: \_\_\_\_\_(yes)  
XXX (No)

CHEMICAL NAME/STRUCTURE: 2-[2-(4-dibenzo [b, f]  
[1,4]thiazepin-11-yl-1-piperazinyl)ethoxy-ethanol  
fumarate(2:1) (salt)  
MW: 883.11 C<sub>22</sub>H<sub>30</sub>N<sub>6</sub>O<sub>4</sub>S<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>



**15. Comments:** These bundled efficacy supplements for Seroquel® Tablets propose a new indication for the treatment of schizophrenia in adolescents (S045) and for the treatment of bipolar mania in children and adolescents (S046). There are no CMC or CMC labeling changes provided in this submission. All CMC is cross-referenced to the original NDA. No environmental assessment is provided in this submission, since the Sponsor claims categorical exclusion, under 21 CFR 25.31. However, an environmental assessment has been submitted by the Sponsor, under Supplement 037 (reviewed as adequate by this reviewer March 5, 2008) which has been evaluated and recommended as FONSI (no significant impact) by Raanan Bloom, Ph.D. (December 11, 2007). The FONSI is valid through 2011.

**16. Conclusions and Recommendations: Adequate.** Since there are no CMC changes and the EA is recommended as FONSI (R. Bloom, Ph.D., December 11, 2007) valid through 2011, then from the CMC standpoint, these sNDAs are recommended for approval.

17. Reviewer Name

Julia C. Pinto, Ph.D., Chemist

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**020639Orig1s046**

**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:** 20-639 / S-045, S-046  
**Drug Name:** Seroquel (quetiapine fumarate)  
**Indication(s):** Children and Adolescents Bipolar I mania and Adolescents Schizophrenia  
**Applicant:** AstraZeneca  
**Date(s):** Received: Oct 28, 2008;  
PDUFA Due Date: Apr 28, 2009  
**Review Priority:** Priority  
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**Keywords:** Clinical studies; NDA review

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# **1. EXECUTIVE SUMMARY**

## **1.1 Conclusions and Recommendations**

The sponsor submitted two short-term studies to seek claims for the efficacy and safety of quetiapine in the treatment of children and adolescent Bipolar I mania and adolescent schizophrenia. Efficacy in Bipolar I mania was demonstrated by the change from baseline to Week 3 in the Young Mania Rating Scale (YMRS) total score. Efficacy in schizophrenia was demonstrated by the change from baseline to Week 6 in the Positive and Negative Symptoms Scale (PANSS) total score.

In both studies, the point estimate of the high dose was observed to be greater than the point estimate of the low dose; however, the difference between the high dose and the low dose was not statistically significant.

## **1.2 Brief Overview of Clinical Studies**

Study D1441C00112 was a 6-week, international, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Quetiapine (400 mg/day and 800 mg/day) were investigated in adolescent schizophrenic patients aged between 13 and 17 years. The randomized sample consisted of 222 patients. The primary endpoint was the change from baseline to Week 6 in the Positive and Negative Symptoms Scale (PANSS) total score.

Study D1441C00149 was a 3-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Bipolar I mania patients between the age of 10 and 17 years enrolled in the study. Two hundreds and eighty-four (284) patients were randomized to either quetiapine 400 mg/day, quetiapine 600 mg/day, or placebo in thirty-four United States centers. The primary endpoint was the change from baseline to Week 3 in the Young Mania Rating Scales (YMRS).

Subjects from studies D1441C00112 and D1441C00149 had an option to participate in an open-label, safety and tolerability extension study D1441C00150. Study D1441C00150 is not a subject of this review.

## **1.3 Statistical Issues and Findings**

Both studies were positive on the primary endpoints. In the Bipolar I mania study, the effects appeared robust for both high dose and low dose. In the schizophrenia study, the effect for low dose appeared weaker and less robust than the high dose. However, in both studies, the difference between the low dose and the high dose was not statistically significant.

## 2. INTRODUCTION

### 2.1 Overview

This review provides a statistical evaluation of quetiapine as a treatment of adolescent schizophrenia and pediatric and adolescent Bipolar I mania.

According to the sponsor, schizophrenia is a neurodevelopmental disorder that affects many aspects of patient's life. Estimates of the lifetime prevalence of schizophrenia range from 0.5% to 1.5%. While onset of schizophrenia before the age of 13 years is rare, the incidence increases steadily during the adolescent years. Adolescents with schizophrenia have significant impairment, including deficits in cognition, affect, and social functioning.

According to the sponsor, Bipolar Disorder is a lifelong psychiatric illness that is characterized by significant morbidity and mortality and is often progressive. Approximately 20% to 40% of adults with Bipolar Disorder report onset during childhood. The estimated prevalence among children and adolescents aged 9 to 17 years is 1.2%. Children and adolescents with bipolar mania have significant social impairment leading to conflict within the family, repeated hospitalization, and increased economic burden on the family. Adolescents with Bipolar Disorder have an increased risk of substance-abuse disorders.

Quetiapine (immediate release) was approved for the treatment of adult schizophrenia in 1997 and adult bipolar mania in 2004. The extended release formulation of quetiapine (quetiapine XR) was approved for the treatment of adult schizophrenia in 2007 and adult bipolar mania in 2008. In February 2003, The Food and Drug Administration (FDA) issued a Written Request (WR) asking AstraZeneca to conduct randomized, double-blind, parallel-group, placebo-controlled efficacy studies in schizophrenic patients aged 13 to 17 years and in Bipolar Disorder patients aged 10 to 17 years. Amendments to the WR were issued in May 2004 and February 2005. This submission contains two studies (one schizophrenia and one Bipolar I mania) to fulfill the Written Requests.

### 2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room:

<\\Cdsub1\evsprod\NDA020639\0006\m5\53-clin-stud-rep\535-rep-ffic-safety-stud>.

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study D1448C00112

##### *3.1.1.1 Objectives*

Primary: The primary objective of this study was to compare the efficacy of 2 doses of quetiapine (400 mg/day and 800 mg/day) with that of placebo in the

treatment of schizophrenia in adolescent patients as assessed by the change from baseline to Day 42 in the PANSS total score.

### 3.1.1.2 Study Design

This was a 6-week, multicenter, double-blind, parallel-group, randomized, placebo-controlled study to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 800 mg/day) with that of placebo in schizophrenic patients aged 13 to 17 years who were either hospitalized or were outpatients. The study consisted of three periods: a screening and washout period of up to 28 days; a randomized, double-blind treatment period of 42 days; and an optional entrance into a 6-month, open-label study of the safety and tolerability of quetiapine. Subjects were titrated to their assigned doses based on the schedule in Table 1.

**Table 1. Study D1448C00112: Quetiapine treatment regimens (mg/day) for administration**

Dose group	Time	Study day										
		1	2	3	4	5	6	7	8	9	10	11-42
400 mg	AM	NA	50	100	100	200	200	200	200	200	200	200
	PM	50	50	100	200	200	200	200	200	200	200	200
800 mg	AM	NA	50	100	100	200	200	300	300	400	400	400
	PM	50	50	100	200	200	300	300	400	400	400	400

AM Morning. NA Not Applicable. PM Evening.  
(Source: d1448c00112 Study Report; Table 5, page 49)

Patients had to have a PANSS total score of at least 60 at screening and baseline; a score of 4 or greater on at least 1 of the following items: delusions, conceptual disorganization, or hallucinations; and a Diagnostic and Statistical Manual of Mental Disorder, 4<sup>th</sup> edition (DSM-IV) diagnosis of schizophrenia. The diagnosis was confirmed by the Schedule of Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (KSADS-PL).

The study was planned for 66 patients per arm to provide 85% power to detect a difference of 15 points change from baseline in the PANSS total score.

### 3.1.1.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from baseline to Day 42 in the PANSS total score. The primary analysis was a mixed effect model for repeated measures (MMRM) with baseline PANSS total score as a covariate, treatment, region, visit, and visit-by-treatment interaction. All effects were considered fixed. An unstructured covariance matrix was used. The Simes-Hommel's approach was used to control the type I error rate. The procedure ordered the p-values obtained from the pair-wise comparison as follows:  $P(1) < P(2)$ . If  $P(2) < 0.05$ , then reject null hypotheses associated with  $P(2)$  and  $P(1)$ . Otherwise, if  $P(1) < 0.025$ , then reject the null hypothesis associated with  $P(1)$ .

Sensitivity analyses on the primary efficacy variable included an ANCOVA model with missing data imputed by the Last Observation Carried Forward (LOCF) method, and an analysis on the per-protocol sample.

### 3.1.1.4 Efficacy Results

#### 3.1.1.4.1 Study Population

The randomized sample consisted of 222 subjects. One hundred and sixty-four subjects (74%) completed the study. The main reasons for dropping out were adverse events, study-specific discontinuation criteria, and patients not willing to continue. Quetiapine groups had higher completion rates than placebo (76.7% and 82.4% compared to 62.7%). There were more subjects dropping out due to adverse events in quetiapine groups than in placebo arm.

**Table 2. Study D1448C00112: Disposition of patients**

	Placebo (N = 75)	QTP 400mg (N = 73)	QTP 800mg (N = 74)	Total (N = 222)
<b>Discontinued study n (%)</b>	<b>28 (37.3)</b>	<b>17 (23.3)</b>	<b>13 (17.6)</b>	<b>58 (26.1)</b>
Adverse event	2 (7.1)	5 (29.5)	7 (53.9)	14 (24.1)
Development of study-specific discontinuation criteria	15 (53.6)	6 (35.3)	2 (15.4)	23 (39.7)
Patient not willing to continue	8 (28.6)	3 (17.7)	3 (23.1)	14 (24.1)
Lost to follow-up	2 (7.1)			2 (3.5)
Other	1 (3.6)	3 (17.7)	1 (7.7)	5 (8.6)
<b>Completed 6-week randomized treatment period</b>	<b>47 (62.7)</b>	<b>56 (76.7)</b>	<b>61 (82.4)</b>	<b>164 (73.9)</b>

(Source: d1448c00112 Study Report; Figure 1, page 96)

The demographic and baseline disease characteristics of the modified intent-to-treat sample are presented in Table 3. The average age was 15.4 years. There were more males than females. Sixty-one percent of the subjects were Caucasians. Orientals and Blacks accounted for about 30% of the sample. The average baseline PANSS total score was 96 and ranged from 46 to 165.5. Across three arms, the demographic and baseline disease characteristics appeared balanced.

**Table 3. Study D1448C00112: Demographic and baseline disease characteristics (MITT sample)**

	Placebo N = 73	QTP 400 mg N = 73	QTP 800 mg N = 74	Total N = 220
<i>Age at entry (yr) n</i>				
Mean (SD)	15.3 (1.4)	15.5 (1.2)	15.4 (1.3)	15.4 (1.3)
Median	16	16	16	16
Min – Max	13 – 17	13 – 17	13 – 17	13 - 17
<i>Sex – n (%)</i>				
Male	42 (57.5)	43 (58.9)	44 (59.5)	129 (58.6)
Female	31 (42.5)	30 (41.1)	30 (40.5)	91 (41.4)
<i>Race – n (%)</i>				
Black	11 (15.1)	7 (9.6)	9 (12.2)	27 (12.3)
Caucasian	46 (63.0)	45 (61.6)	44 (59.5)	135 (61.4)
Oriental	12 (16.4)	15 (20.6)	13 (17.6)	40 (18.2)
Others	4 (5.5)	6 (8.2)	8 (10.8)	18 (8.2)
<i>Baseline BMI (kg/m<sup>2</sup>)</i>				
Mean (SD)	22.7 (4.7)	21.8 (5.6)	22.5 (4.7)	22.3 (5.0)
Min – Max	15.4 – 40.0	14.5 – 41.3	13.5 – 37.2	13.5 – 41.3
<i>Baseline PANSS-total score</i>				
N	72	73	74	219
Mean (SD)	96.2 (17.7)	96.2 (17.7)	96.9 (15.3)	96.4 (16.8)
Median	94.5	93	93	94
Min – Max	60 – 165.5	46 – 135	69 – 137	46 – 165.5

(Source: d1448c00112 Study Report; Tables 22 & 11.2.1.1.1, pages 100 & 328)

#### 3.1.1.4.2 Sponsor's Efficacy Results for Primary Endpoint

The sponsor's primary efficacy analysis is summarized in Table 4. Using the Simes-Hommel's adjustment for multiplicity, both quetiapine 400 mg/day and quetiapine 800 mg/day were statistically significantly superior to placebo.

**Table 4. Study D1448C00112: Sponsor's primary efficacy results: change from randomization to week 6 in the PANSS total score (MMRM) in the MITT sample**

	Placebo	QTP 400mg	QTP 800mg
Sample size at Week 6	43	54	55
LS Means	-19.15	-27.31	-28.44
Difference from placebo		-8.16	-9.29
(95% confidence interval)		(-16.06, -0.26)	(-16.22, -2.36)
Unadjusted p-values		0.043	0.009

(Source: d1448c00112 Study Report; Table 25, page 110)

#### 3.1.1.4.3 Sponsor's Other Efficacy Results

**Primary sensitivity analyses:** Table 5 summarizes the primary efficacy variable analyzed using an ANCOVA model with missing values imputed by the LOCF method. The results corroborated with the primary findings in Table 4.

**Table 5. Study D1448C00112: Sponsor’s primary sensitivity analysis: change from randomization to week 6 in the PANSS total score (LOCF) in the MITT sample**

	Placebo	QTP 400mg	QTP 800mg
Sample size	73	73	74
LS Means	-18.52	-25.76	-27.23
Difference from placebo (95% confidence interval)		-7.24 (-14.02, -0.47)	-8.71 (-15.45, -1.96)
Unadjusted p-values		0.036	0.012

(Source: d1448c00112 Study Report; Table 11.2.1.2.3, page 334)

\*The sample sizes in Table 5 are larger than in Table 7 at Day 07 due to three subjects who didn’t have visits Day 07 and Day 14 assessments (subjects (b) (6) 2 and ID (b) (6) did not have assessment visits Day 07 and Day 14, subject (b) (6) did not have assessment visit Day 07).

The results in Table 4 were repeated for the per-protocol (PP) sample. Both quetiapine groups showed a numerical improvement over placebo. However, the differences between each quetiapine group and placebo were smaller and were not statistically significant.

**Table 6. Study D1448C00112: Sponsor’s primary sensitivity analysis: change from randomization to week 6 in the PANSS total score (MMRM) in the PP sample**

	Placebo	QTP 400mg	QTP 800mg
Sample size at Week 6	32	44	46
LS Means	-21.28	-26.77	-27.99
Difference from placebo (95% confidence interval)		-5.49 (-14.15, 3.16)	-6.72 (-14.48, 1.05)
Unadjusted p-values		0.212	0.090

(Source: d1448c00112 Study Report; Table 11.2.1.2.2, page 333)

An analysis on the primary endpoint over time (MMRM):

Table 7 summarizes the treatment effect over time based on an MMRM analysis. The treatment effects appeared to be more consistent for quetiapine 800mg/day dose group than for the quetiapine 400mg/day dose group.

**Table 7. Study D1448C00112: Sponsor’s efficacy analysis: change from randomization in the PANSS total score (MMRM) over time in the MITT sample**

Visit	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
	N	Mean	N	Mean	N	Mean	Diff	P-value*	Diff	P-value*
Day 07	72	-6.65	73	-8.23	72	-8.80	-1.58	0.410	-2.16	0.214
Day 14	72	-10.09	70	-14.24	71	-16.09	-4.15	0.098	-6.00	0.012
Day 21	65	-12.14	67	-20.37	68	-19.42	-8.23	0.006	-7.28	0.011
Day 28	57	-15.00	59	-22.72	65	-22.38	-7.72	0.023	-7.39	0.018
Day 35	51	-18.00	59	-24.68	62	-26.14	-6.68	0.085	-8.14	0.019
Day 42	43	-19.15	54	-27.31	55	-28.44	-8.16	0.043	-9.29	0.009

(Source: d1448c00112 Study Report; Table 11.2.1.2.1, page 332)

\*p-values are not adjusted for multiplicity

Change from baseline in the CGI-Severity of Illness (MMRM):

The change from baseline over time in the CGI-Severity of Illness score was analyzed via an MMRM analysis similar to the primary analysis model. The model included the baseline CGI-S score, treatment, region, visit, and visit-by-treatment interactions. The model utilized an unstructured covariance matrix. The results are summarized in Table 8. The responses did not appear to be consistent for the 400 mg/day dose and did not reach a statistically significant level at the endpoint visit (Week 6). The high dose (800 mg/day) appeared more consistently superior to placebo over time and achieved the 0.05 significant level at Week 6.

**Table 8. Study D1448C00112: Sponsor’s secondary analysis: change from randomization in the CGI-S score (MMRM) in the MITT sample**

Visit	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
	N	Mean	N	Mean	N	Mean	Diff	P-value*	Diff	P-value*
Day 07	72	-0.18	73	-0.32	72	-0.35	-0.13	0.226	-0.17	0.061
Day 14	72	-0.40	70	-0.56	71	-0.74	-0.17	0.220	-0.34	0.006
Day 21	65	-0.52	66	-0.81	68	-0.78	-0.30	0.065	-0.26	0.060
Day 28	57	-0.64	60	-0.96	65	-0.99	-0.32	0.084	-0.35	0.039
Day 35	51	-0.88	59	-1.10	62	-1.16	-0.22	0.250	-0.28	0.113
Day 42	43	-0.81	55	-1.15	55	-1.28	-0.34	0.104	-0.47	0.018

(Source: d1448c00112 Study Report; Table 11.2.3.2.1.3, page 410)

\*p-values are not adjusted for multiplicity

*3.1.1.4.4 Reviewer’s Results and Comments*

This reviewer confirms the findings based on the primary efficacy variable as presented in Table 4. Both doses of quetiapine were statistically significantly better than placebo.

This reviewer performed an analysis based on an ANCOVA model with dropouts imputed by the LOCF method. The model included treatment, region, and baseline PANSS total score. The results were slightly different from those presented by the sponsor in Table 5, but did not affect the outcome of the trial.

**Table 9. Study D1448C00112: Reviewer’s primary sensitivity analysis: change from randomization to week 6 in the PANSS total score (LOCF) in the MITT sample**

	Placebo	QTP 400mg	QTP 800mg
Sample size	73	73	74
LS Means	-18.53	-26.09	-27.23
Difference from placebo (95% confidence interval)		-7.55 (-14.26, -0.85)	-8.70 (-15.37, -2.02)
Unadjusted p-values		0.027	0.011

(Source: Reviewer’s results)

Two sensitivity analyses were pre-specified. One was based on the same analysis model as the primary analysis on the per-protocol population. This analysis showed that both doses of quetiapine were numerically better than placebo.

However, the numerical differences did not reach the statistically significant level. The other sensitivity analysis was an ANCOVA model with missing data imputed by the LOCF method. This analysis corroborated with the primary findings. An analysis on the CGI-Severity of Illness score showed superiority of the quetiapine 800mg/day dose group over placebo, but not on the 400 mg/day dose group.

One subject (ID # [REDACTED]<sup>(b) (6)</sup>) did not appear to have the baseline evaluation or the baseline evaluation visit was miscoded. Removing this subject did not affect the outcome of the study.

Investigator John Gilliam (Site # 10) enrolled 6 subjects. The results of the primary analysis excluding Site # 10 remained statistically significant (p-value = 0.042 for the comparison between quetiapine 400 mg/day versus placebo and p-value = 0.012 for the comparison between quetiapine 800 mg/day versus placebo).

In summary, this study demonstrated the efficacy of quetiapine 400 mg/day and 800 mg/day over placebo on the change from baseline to Week 6 in the PANSS total score. The effect appeared more robust for the 800 mg/day dose group than the 400 mg/day dose group. The 800 mg/day dose group appeared numerically more efficacious than the 400 mg/day; however, the numerical difference was small and did not appear statistically meaningful.

### **3.1.2 Study D1448C00149**

#### *3.1.2.1 Objectives*

Primary: The primary objective of this study was to compare the efficacy of 2 doses of quetiapine (400 mg/day and 600 mg/day) with that of placebo in the treatment of Bipolar mania in children and adolescent patients with Bipolar I Disorder, as assessed by the change from baseline to Day 21 in the Young Mania Rating Scale (YMRS) total score.

#### *3.1.2.2 Study Design*

This was a 3-week, randomized, double-blind, multi-center, parallel-group, placebo-controlled study. The study was to investigate the efficacy and safety of two fixed doses of quetiapine (400 mg/day and 600 mg/day) and placebo, in divided dosing (either twice daily or three times daily, per the judgment of the investigator). The study consisted of three periods: 1) a screening and washout period that lasted up to 28 days; 2) a randomized, double-blind period of 21 days; 3) an optional entrance into a 6-month, open-label study. Subjects were randomized in a 1:1:1 ratio to 1 of the 3 treatment groups. They could be treated as inpatient or outpatient. Patients initiated the treatment at a 50 mg/day and were titrated to their assigned dosages using the following schedule:

**Table 10. Study D1448C00149: Quetiapine treatment regimens (mg/day) for administration twice daily**

Dose group	Time	Study day										
		1	2	3	4	5	6	7	8	9	10	11-21
400mg	AM	NA	50	100	100	200	200	200	200	200	200	200
	PM	50	50	100	200	200	200	200	200	200	200	200
600mg	AM	NA	50	100	100	200	200	300	300	300	300	300
	PM	50	50	100	200	200	300	300	300	300	300	300

AM Morning. NA Not Applicable. PM Evening.

(Source: d1448c00149 Study Report; Table 5, page 49)

Male and female patients between the age of 10 and 17 were eligible to participate in the study. Patients, diagnosed with a DSM-IV Bipolar I mania, had to have an YMRS score of  $\geq 20$  both at screening and at randomization to enroll. The diagnosis was confirmed by the K-SADS-PL.

The study was planned for 88 patients per arm to provide 85% power to detect a difference of 6 points change from baseline in the YMRS total score.

### 3.1.2.3 Efficacy Endpoints and Analyses

**Primary endpoint and analysis:** The primary endpoint was the change from baseline to Day 21 in the YMRS total score. The primary analysis was a mixed model for repeated measures (MMRM). Covariates included age stratum, treatment, visit, visit-by-treatment interaction, and baseline YMRS total score. All of these effects were considered as fixed effects. An unstructured covariance pattern was used. Robust variance estimates for the fixed effects were used for testing the treatment differences. The Simes-Hommel's approach was used to control the type I error rate. The procedure ordered the p-values obtained from the pair-wise comparison as follows:  $P(1) < P(2)$ . If  $P(2) < 0.05$  then reject null hypotheses associated with  $P(2)$  and  $P(1)$ . Otherwise, if  $P(1) < 0.025$ , then reject the null hypothesis associated with  $P(1)$ .

### 3.1.2.4 Efficacy Results

#### 3.1.2.4.1 Study Population

The randomized sample consisted of 284 subjects. Seventy-eight percent of the subjects completed the study. The main reason for dropping out was adverse event. There were more adverse events in quetiapine arms than in placebo arm. There were more patients dropping out due to lack of efficacy in the placebo arm than in the quetiapine arms.

**Table 11. Study D1448C00149: Disposition of Patients**

	Placebo (N = 91)	QTP 400mg (N = 95)	QTP 600mg (N = 98)	Total (N = 284)
<b>Discontinued study: n (%)</b>	<b>25 (27.5)</b>	<b>19 (20.0)</b>	<b>18 (18.4)</b>	<b>62 (21.8)</b>
Adverse event	4 (16.0)	15 (79.0)	7 (38.9)	26 (41.9)
Development of study-specific discontinuation criteria	4 (16.0)	1 (5.3)	2 (11.1)	7 (11.3)
Patient not willing to continue	5 (20.0)	1 (5.3)	5 (27.8)	11 (17.7)
Lost to follow-up	2 (8.0)	0 (0.0)	1 (5.6)	3 (4.8)
Lack of efficacy	6 (24.0)	2 (10.5)	0 (0.0)	8 (12.9)
Other	4 (16.0)	0 (0.0)	3 (16.7)	7 (11.3)
<b>Completed 3-week randomized treatment phase</b>	<b>66 (72.5)</b>	<b>76 (80.0)</b>	<b>80 (81.6)</b>	<b>222 (78.2)</b>

(Source: d1448c00149 Study Report; Figure 1, page 95 and reviewer's results)

The demographic and baseline disease characteristics of the MITT sample are presented in Table 12. The average age was 13 years old. There were slightly more males than females. Caucasians accounted for about 77% of the sample and Blacks accounted for about 14% of the sample. The baseline YMRS total score was 30 on average and ranged from 12 to 48.

**Table 12. Study D1448C00149: Demographic and baseline disease characteristics (MITT sample)**

	Placebo N = 89	QTP 400 mg N = 93	QTP 600 mg N = 95	Total N = 277
<i>Age at entry (yr) n</i>				
Mean (SD)	13.31 (2.14)	13.11 (2.16)	13.15 (2.18)	13.19 (2.16)
Median	13	13	13	13
Min – Max	10 – 17	10 – 17	9 – 17	9 – 17
<i>Sex – n (%)</i>				
Male	54 (60.7)	47 (50.5)	55 (57.9)	156 (56.3)
Female	35 (39.3)	46 (49.5)	40 (42.1)	121 (43.7)
<i>Race – n (%)</i>				
Black	12 (13.5)	12 (12.9)	14 (14.7)	38 (13.7)
Caucasian	66 (74.2)	73 (78.5)	73 (76.8)	212 (76.5)
Oriental	1 (1.1)			1 (0.4)
Others	10 (11.2)	8 (8.6)	8 (8.4)	26 (9.4)
<i>BMI at baseline (kg/m<sup>2</sup>)</i>				
Mean (SD)	24.14 (5.67)	23.50 (5.31)	23.38 (4.77)	23.67 (5.25)
Min – Max	14.3 – 41.1	12.2 – 38.6	16.2 – 35.2	12.2 – 41.1
<i>Baseline YMRS-total score*</i>				
N	89	92	95	276
Mean (SD)	30.65 (5.89)	29.45 (5.84)	29.62 (6.35)	29.89 (6.03)
Median	30	29	29	29
Min – Max	21 – 48	12 – 44	20 – 46	12 – 48

(Source: d1448c00149 Study Report; Table 21, page 99)

\* Reviewer's results

#### 3.1.2.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary analysis model was a mixed model for repeated measures with model terms treatment, visit, treatment-by-visit interaction, baseline YMRS total score, and age stratum. Age at entry was dichotomized to two strata: 10-12 years

old and 13-17 years old. According to the statistical analysis plan, randomization numbers 3001-4500 were allocated to 10-12 years old group. Randomization numbers 4501-6000 were allocated to 13-17 years old group. If patients were randomized to a wrong stratum, the patients were analyzed as randomized. The sponsor's primary analysis is summarized in Table 13. Both doses of quetiapine were statistically significantly superior to placebo.

**Table 13. Study D1448C00149: Sponsor's primary analysis: change from randomization to week 3 in the YMRS total score (MMRM) in the MITT sample**

	Placebo	QTP 400mg	QTP 600mg
Sample size at Week 3	67	76	81
LS Means	-9.04	-14.25	-15.06
Difference from placebo (95% confidence interval)		-5.21 (-8.11, -2.31)	-6.56 (-9.48, -3.65)
Unadjusted p-values		<0.001	<0.001

(Source: d1448c00149 Study Report; Table 24, page 111)

#### 3.1.1.4.3 Sponsor's Other Efficacy Results

A primary sensitivity analysis (PP): The primary analysis model was repeated using the per-protocol population. The results are summarized in Table 14. This analysis corroborated with the primary analysis presented in Table 13.

**Table 14. Study D1448C00149: Sponsor's sensitivity primary analysis: change from baseline to week 3 in the YMRS total score (MMRM) in the PP sample**

	Placebo	QTP 400mg	QTP 600mg
Sample size at Week 3	55	60	69
LS Means	-9.60	-15.50	-16.57
Difference from placebo (95% confidence interval)		-5.90 (-9.09, -2.72)	-6.98 (-10.14, -3.81)
Unadjusted p-values		<0.001	<0.001

(Source: d1448c00149 Study Report; Table 11.2.1.2.2, page 368)

A primary sensitivity analysis (LOCF, MITT): An ANCOVA model with missing data imputed by the LOCF method is summarized in Table 15. This analysis also corroborated with the primary analysis presented in Table 13.

**Table 15. Study D1448C00149: Sponsor's sensitivity primary analysis: change from baseline to week 3 in the YMRS total score (LOCF) in the MITT sample**

	Placebo	QTP 400mg	QTP 600mg
Sample size	89	93	95
LS Means	-8.28	-13.42	-15.18
Difference from placebo (95% confidence interval)		-5.15 (-7.93, -2.36)	-6.90 (-9.66, -4.13)
Unadjusted p-values		<0.001	<0.001

(Source: d1448c00149 Study Report; Table 11.2.1.2.3, page 369)

An analysis on the primary endpoint over time (MMRM): The treatment effects of quetiapine over the duration of the study are summarized in Table 16. The effects appeared consistent over the three weeks of the study. It is noted that many placebo patients did not have Visit Day 04 evaluated.

**Table 16. Study D1448C00149: Sponsor’s efficacy analysis: change from randomization in the YMRS total score (MMRM) over time in the MITT sample**

Visit	Placebo		QTP 400mg		QTP 600mg		QTP400mg - Pbo		QTP600mg - Pbo	
	n	Mean	n	Mean	n	Mean	Diff	P-value*	Diff	P-value*
Day 04	64	-5.01	81	-8.05	75	-6.84	-3.05	0.015	-1.83	0.120
Day 07	84	-6.78	88	-11.88	90	-11.83	-5.10	<0.001	-5.05	<0.001
Day 14	73	-8.47	79	-13.26	82	-14.76	-4.79	0.001	-6.29	<0.001
Day 21	67	-9.04	76	-14.25	81	-15.60	-5.21	<0.001	-6.56	<0.001

(Source: d1448c00149 Study Report; Table 11.2.1.2.1, page 367)

\*p-values are not adjusted for multiplicity

*3.1.2.4.4 Reviewer’s Results and Comments*

This reviewer confirmed the results based on the primary endpoint as presented in Table 13. Quetiapine 400 mg/day and 600 mg/day were statistically superior to placebo in the change from baseline to Day 21 in the YMRS total score.

There were 5 patients who were randomized to a wrong age stratum. The primary analysis was re-analyzed using age group as defined by 10-12 years old versus 13-17 years old. Table 17 summarizes this analysis. Both doses of quetiapine were statistically significant based on this analysis.

**Table 17. Study D1448C00149: Reviewer’s analysis: change from randomization to week 3 in the YMRS total score (MMRM) in the MITT sample**

	Placebo	QTP 400mg	QTP 600mg
Sample size at Week 3	67	76	81
LS Means	-9.03	-14.25	-15.60
Difference from placebo		-5.23	-6.57
(95% confidence interval)		(-8.13, -2.32)	(-9.49, -3.66)
Unadjusted p-values		0.001	<0.001

(Source: reviewer’s results)

The reviewer’s ANCOVA analysis with dropouts imputed by the LOCF method deviated slightly from the sponsor’s results in Table 15. The deviations did not affect the outcome of the study.

**Table 18. Study D1448C00149: Reviewer’s sensitivity primary analysis: change from baseline to week 3 in the YMRS total score (LOCF) in the MITT sample**

	Placebo	QTP 400mg	QTP 600mg
Sample size	89	93	95
LS Means	-8.39	-13.63	-15.16
Difference from placebo		-5.24	-6.77
(95% confidence interval)		(-8.01, -2.47)	(-9.53, -4.02)
Unadjusted p-values		<0.001	<0.001

(Source: Reviewer’s results)

Investigator John Gilliam (Site # 10) randomized 26 subjects. The results of the primary analysis excluding Site # 10 remained statistically significant (p-values < 0.001 for both dose groups).

In summary, Study D1448C00149 demonstrated the efficacy of quetiapine at 400 mg/day and 600 mg/day in lowering the YMRS total score from baseline at Week 3. The 600 mg/day dose group showed a numerical greater benefit than the 400 mg/day dose group; however, the difference did not appear to be statistically meaningful.

### 3.2 Evaluation of Safety

Please refer to the clinical review for extensive safety evaluation and report. The following sections explore the effects of quetiapine on body weight and body mass.

#### 3.2.1 Study D1448C00112

To explore the effects of quetiapine on body weight and body mass, this reviewer carried out two exploratory analyses. The first analysis was on the change from baseline in the body weight (in kg). The second analysis was on the change from baseline in the body mass index (BMI) (in kg/m<sup>2</sup>). Repeated measures mixed effect models with baseline body weight or BMI, treatment, region, visit, sex, race, age at entry, and treatment-by-visit interaction as fixed factors were used. The models used unstructured covariance matrices. The results are summarized in Table 19 and Table 20. The results suggested that patients on quetiapine appeared to gain significantly more weights than patients on placebo.

**Table 19. Study D1448C00112: Reviewer's exploratory analysis: change from randomization in the Body Weight (MMRM) in the Safety sample**

Visit	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
	N	Mean	N	Mean	N	Mean	Diff	P-value*	Diff	P-value*
Day 07	72	-0.22	73	0.31	72	0.33	0.53	0.014	0.55	0.012
Day 14	72	-0.11	70	1.06	71	0.63	1.17	<0.001	0.74	0.010
Day 21	65	-0.14	67	1.23	68	0.89	1.38	<0.001	1.03	0.003
Day 28	57	-0.35	61	1.40	65	1.05	1.76	<0.001	1.40	0.001
Day 35	51	-0.32	58	1.73	62	1.51	2.05	<0.001	1.83	<0.001
Day 42	44	-0.33	56	1.96	55	1.53	2.30	<0.001	1.86	0.001

(Source: Reviewer's results)

\*p-values are not adjusted for multiplicity

**Table 20. Study D1448C00112: Reviewer’s exploratory analysis: change from randomization in the BMI (MMRM) in the Safety sample**

Visit	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
	N	Mean	N	Mean	N	Mean	Diff	P-value*	Diff	P-value*
Day 07	72	-0.06	73	0.13	72	0.14	0.19	0.014	0.20	0.017
Day 14	72	-0.03	70	0.38	71	0.22	0.41	<0.001	0.25	0.023
Day 21	65	-0.04	67	0.43	68	0.30	0.47	<0.001	0.34	0.010
Day 28	57	-0.13	61	0.48	65	0.33	0.60	<0.001	0.46	0.003
Day 35	51	-0.11	58	0.56	62	0.47	0.67	<0.001	0.57	0.001
Day 42	44	-0.15	56	0.63	55	0.45	0.78	<0.001	0.61	0.002

(Source: Reviewer’s results)

\*p-values are not adjusted for multiplicity

### 3.2.2 Study D1448C00149

To explore the effects of quetiapine on body weight and body mass, this reviewer carried out two exploratory analyses. The first analysis was on the change from baseline in the body weight (in kg). The second analysis was on the change from baseline in the body mass index (BMI) (in kg/m<sup>2</sup>). The models utilized were similar to the primary analysis model with baseline body weight or BMI as fixed covariates, age group, sex, race, treatment, visit, and treatment-by-visit interaction as fixed factors. The models used unstructured covariance matrices. The results are summarized in Table 21 and Table 22. The results suggested that patients on quetiapine appeared to gain significantly more weights than patients on placebo.

**Table 21. Study D1448C00149: Reviewer’s exploratory analysis: change from randomization in the Body Weight (MMRM) in the Safety sample**

Visit	Placebo		QTP 400mg		QTP 600mg		QTP400mg - Pbo		QTP600mg - Pbo	
	N	Mean	N	Mean	N	Mean	Diff	P-value*	Diff	P-value*
Day 04	64	0.03	80	0.58	73	0.35	0.55	0.009	0.32	0.060
Day 07	85	0.16	88	0.86	90	0.88	0.69	<0.001	0.71	0.001
Day 14	73	0.13	78	1.31	82	1.29	1.18	<0.001	1.16	<0.001
Day 21	68	0.11	76	1.67	81	1.54	1.56	<0.001	1.43	<0.001

(Source: Reviewer’s results)

\*p-values are not adjusted for multiplicity

**Table 22. Study D1448C00149: Reviewer’s exploratory analysis: change from randomization in the BMI (MMRM) in the Safety sample**

Visit	Placebo		QTP 400mg		QTP 600mg		QTP400mg - Pbo		QTP600mg - Pbo	
	N	Mean	N	Mean	N	Mean	Diff	P-value*	Diff	P-value*
Day 04	64	0.03	80	0.24	73	0.14	0.21	0.012	0.11	0.128
Day 07	85	0.06	88	0.32	90	0.26	0.26	0.001	0.20	0.020
Day 14	73	0.01	78	0.48	82	0.43	0.47	<0.001	0.42	<0.001
Day 21	68	0.00	76	0.56	81	0.48	0.56	<0.001	0.48	<0.001

(Source: Reviewer’s results)

\*p-values are not adjusted for multiplicity

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

#### 4.1.1 Study D1448C00112

##### 4.1.1.1 Gender

The primary analysis stratified by gender is presented in Table 23. Quetiapine appeared to improve the PANSS total score for both males and females.

**Table 23. Study D1448C00112: Sponsor's primary efficacy results by gender: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample**

	Placebo	QTP 400mg	QTP 800mg
<i>Females</i>			
Sample size at Week 6	15	19	19
LS Means	-16.14	-26.05	-25.92
Difference from placebo (95% confidence interval)		-9.91 (-23.03, 3.20)	-9.78 (-20.75, 1.19)
<i>Males</i>			
Sample size at Week 6	28	35	36
LS Means	-20.78	-27.99	-29.47
Difference from placebo (95% confidence interval)		-7.21 (-17.34, 2.92)	-8.68 (-17.82, 0.46)

(Source: Reviewer's results)

##### 4.1.1.2 Race

Due to small sample sizes, race was dichotomized to Caucasian versus other races. Quetiapine showed numerical improvements in the PANSS total score in both race groups.

**Table 24. Study D1448C00112: Reviewer's primary efficacy results by race: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample**

	Placebo	QTP 400mg	QTP 800mg
<i>Caucasians</i>			
Sample size at Week 6	24	33	31
LS Means	-16.79	-23.24	-24.79
Difference from placebo (95% confidence interval)		-6.45 (-16.94, 4.03)	-8.01 (-17.45, 1.43)
<i>Others</i>			
Sample size at Week 6	19	21	24
LS Means	-25.04	-35.33	-34.99
Difference from placebo (95% confidence interval)		-10.29 (-22.50, 1.92)	-9.95 (-20.54, 0.65)

(Source: Reviewer's results)

#### 4.1.1.3 Age

Age at entry was dichotomized to  $\leq 15$  versus  $> 15$  years old. The primary analysis stratified by age at entry is summarized in Table 25. Quetiapine appeared to be more efficacious for subjects under the age of 15 years. For subjects  $> 15$  years old, the relative efficacy of quetiapine versus placebo appeared diminished by the large placebo effect.

**Table 25. Study D1448C00112: Reviewer’s primary efficacy results by age: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample**

	Placebo	QTP 400mg	QTP 800mg
<i>Age at entry <math>\leq 15</math></i>			
Sample size at Week 6	20	23	23
LS Means	-12.18	-28.43	-28.71
Difference from placebo (95% confidence interval)		-16.26 (-28.27, -4.24)	-16.53 (-26.19, -6.87)
<i>Age at entry <math>&gt; 15</math></i>			
Sample size at Week 6	23	31	32
LS Means	-25.72	-25.76	-27.91
Difference from placebo (95% confidence interval)		-0.04 (-10.40, 10.32)	-2.18 (-12.07, 7.70)

(Source: Reviewer’s results)

#### 4.1.2 Study D1448C00149

##### 4.1.2.1 Gender

Table 26 summarizes the primary analysis stratified by gender. Treatment benefits were observed in both males and females.

**Table 26. Study D1448C00149: Sponsor’s primary efficacy results by gender: change from baseline to week 3 in the YMRS total score (MMRM) in the MITT sample**

	Placebo	QTP 400mg	QTP 600mg
<i>Females</i>			
Sample size at Week 3	26	36	31
LS Means	-9.52	-15.27	-14.67
Difference from placebo (95% confidence interval)		-5.75 (-9.84, -1.67)	-5.15 (-9.53, -0.76)
<i>Males</i>			
Sample size at Week 3	41	40	50
LS Means	-8.64	-13.46	-16.23
Difference from placebo (95% confidence interval)		-4.82 (-8.90, -0.74)	-7.59 (-11.54, -3.65)

(Source: Reviewer’s results)

##### 4.1.2.2 Race

Table 27 summarizes the primary analysis by race. Due to small sample sizes, race was dichotomized into Caucasians versus other races. Treatment effects were observed in both groups.

**Table 27. Study D1448C00149: Sponsor’s primary efficacy results by race: change from baseline to week 3 in the YMRS total score (MMRM) in the MITT sample**

	Placebo	QTP 400mg	QTP 600mg
<i>Caucasians</i>			
Sample size at Week 3	50	60	60
LS Means	-8.61	-13.72	-15.95
Difference from placebo (95% confidence interval)		-5.10 (-8.42, -1.79)	-7.34 (-10.74, -3.94)
<i>Others</i>			
Sample size at Week 3	17	16	21
LS Means	-10.82	-16.45	-14.66
Difference from placebo (95% confidence interval)		-5.63 (-11.48, 0.22)	-3.84 (-9.38, 1.69)

(Source: Reviewer’s results)

#### 4.1.2.3 Age

Table 28 summarizes the primary analysis stratified by age groups. Treatment effects were observed in both quetiapine dose groups.

**Table 28. Study D1448C00149: Sponsor’s primary efficacy results by age: change from baseline to week 3 in the YMRS total score (MMRM) in the MITT sample**

	Placebo	QTP 400mg	QTP 600mg
<i>Age 10-12</i>			
Sample size at Week 3	26	32	37
LS Means	-8.68	-13.49	-17.06
Difference from placebo (95% confidence interval)		-4.81 (-9.73, 0.12)	-8.38 (-13.05, -3.71)
<i>Age 13 - 17</i>			
Sample size at Week 3	41	44	44
LS Means	-9.35	-14.92	-14.39
Difference from placebo (95% confidence interval)		-5.57 (-9.18, -1.96)	-5.04 (-8.83, -1.24)

(Source: Reviewer’s results)

## 4.2 Other Subgroups

### 4.2.1 Study D1448C00112

#### 4.2.1.1 U.S.A. versus non-U.S.A.

The primary efficacy analysis stratified by U.S.A. versus non-U.S.A. is presented in Table 29. Quetiapine appeared to show greater improvement among U.S.A. patients than non-U.S.A. patients.

**Table 29. Study D1448C00112: Sponsor's primary efficacy results by region: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample**

	Placebo	QTP 400mg	QTP 800mg
<i>U.S.A.</i>			
Sample size at Week 6	14	15	15
LS Means	-20.69	-38.50	-38.45
Difference from placebo (95% confidence interval)		-17.81 (-33.83, -1.78)	-17.75 (-32.30, -3.20)
<i>Non-U.S.A.</i>			
Sample size at Week 6	29	39	40
LS Means	-19.33	-22.71	-23.89
Difference from placebo (95% confidence interval)		-3.38 (-11.91, 5.15)	-4.56 (-11.81, 2.70)

(Source: Reviewer's results)

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

Both studies were positive on the primary endpoints. In the Bipolar I mania study, the effects appeared robust for both high dose and low dose. In the schizophrenia study, the effect for low dose appeared weaker and less robust than the high dose. However, in both studies, the difference between the low dose and the high dose was not statistically significant.

### 5.2 Conclusions and Recommendations

The sponsor submitted two short-term studies to seek claims for the efficacy and safety of quetiapine in the treatment of children and adolescent Bipolar I mania and adolescent schizophrenia. Efficacy in Bipolar I mania was demonstrated by the change from baseline to Week 3 in the Young Mania Rating Scale (YMRS) total score. Efficacy in schizophrenia was demonstrated by the change from baseline to Week 6 in the Positive and Negative Symptoms Scale (PANSS) total score.

In both studies, the point estimate of the high dose was observed to be greater than the point estimate of the low dose; however, the difference between the high dose and the low dose was not statistically significant.

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James Hung  
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**020639Orig1s046**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology and Biopharmaceutics Review

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NDA:	20639 SE5-045/046
Drug:	Quetiapine fumarate
Trade Name:	Seroquel®
Indication:	Treatment of schizophrenia and bipolar mania in pediatric patients
Sponsor:	Astra-Zeneca
Submission Type:	Pediatric Efficacy Supplement
Submission Date:	10/28/08, 10/30/08,10/31/08, 2/27/09
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## **1. Executive Summary**

### **1.1 Recommendations**

The Office of Clinical Pharmacology has reviewed the data submitted to the Clinical Pharmacology section of this supplemental NDA and finds it acceptable. The following are the general conclusions from the data OCP reviewed:

1. There was a tendency for children aged 10 -12 years old to have higher exposures of quetiapine (AUC was 36% – 55% and Cmax was 54% - 71% higher) than adolescents aged 13 to 17 years old.
2. Dose normalized exposures were generally lower (AUC = 12% lower and Cmax = 8% lower) in pediatric/adolescent patients than adult. These differences are not expected to be clinically relevant.
3. Dose normalized, weight-normalized AUC and Cmax decreased by about 40% when pediatric children ages 10 to 17 were compared to adults. The decrease in exposure are not expected to be clinically relevant.
4. Quetiapine does not appear to prolong QTc interval in children and adolescents at the proposed clinical doses.

### **1.2 Phase IV Commitments recommended**

There are no phase IV recommendations from OCP

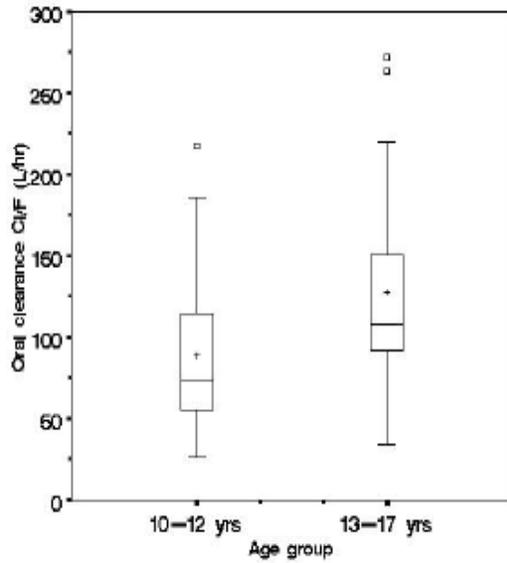
### **1.3 Summary of Clinical Pharmacology Findings**

*Background:* In response to a Written Request issued by the Agency, the sponsor submitted a supplemental New Drug Administration containing, pharmacokinetic, efficacy and safety data for the use of Seroquel in the treatment of schizophrenia and bipolar mania in pediatric patients.

*Comparison of exposures between pediatric patients aged 10 -17 years old.*

In a pharmacokinetic study in which pharmacokinetic data was obtained on days 7 and 13 of dosing, exposure to quetiapine in terms of AUC<sub>ss</sub> and C<sub>ss,max</sub> appeared to be higher in 10- to 12-year-old subjects than in the 13- to 17-year-old subjects. The geometric means for AUC<sub>ss</sub> on Days 7 and 13 were 55% and 36% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 – 17 year old. The geometric means for C<sub>ss,max</sub> on Days 7 and 13 were 71% and 54% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 -17 year olds. The apparent oral clearance (CL/F) was 38% and 30% lower for the 10- to 12-year-old subjects on Days 7 and 13, respectively as compared to 13 to 17 year olds.

Figure 1: Box plots of oral clearance of quetiapine on Day 7 and Day 13 by age group



Note: The horizontal lines in the graph indicate the 10th,25th,50th,75th,and 90th percentiles

*Comparison of exposures between pediatric patients aged 10 -17 years and Adults.*

Comparison of dose normalized exposures (AUCss and Cmax) to quetiapine showed a 12% decrease in exposure (AUC) in pediatric children ages 10 to 17 years old compared to adults. Approximately a 40% decrease in AUC was also observed when exposures were adjusted for dose and weight of patients. The decrease in exposure may not be clinically relevant.

Table 1: Comparison of dose-normalized exposure (AUCss and Cmax) to quetiapine and 3 metabolites in children/adolescents with exposure in adults

Analyte	Dose-normalized AUC <sub>ss</sub>		Dose-normalized C <sub>ss,max</sub>	
	Mean ratio <sup>a</sup>	90% CI	Mean ratio <sup>a</sup>	90% CI
Quetiapine	0.88	0.76, 1.03	0.92	0.79, 1.06
Quetiapine sulfoxide	1.27	1.15, 1.39	1.30	1.16, 1.44
7-hydroxy quetiapine	1.08	0.92, 1.26	1.11	0.94, 1.31
N-desalkyl quetiapine	1.45	1.30, 1.61	1.31	1.15, 1.49

<sup>a</sup> Ratio (10- to 17-year-olds:adults) of least squares means from ANOVA model.

ANOVA analysis of variance. AUC<sub>ss</sub>, area under the curve at steady-state. CI confidence interval. C<sub>ss,max</sub> maximum plasma concentration at steady-state.

Table 2: Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites in children/adolescents with exposure in adults

Analyte	Dose- Weight Normalized AUC		Dose -Weight normalized Cmax	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	0.59	0.50 – 0.70	0.61	0.53 – 0.72
Quetiapine sulfoxide	0.85	0.77 – 0.93	0.86	0.79 – 0.95
7-hydroxy quetiapine	0.72	0.61 – 0.84	0.74	0.63 – 0.87
N-desalkyl quetiapine	0.96	0.86 – 1.07	0.87	0.76 – 1.00

Figure 2: Box plot of Dose-normalized, weight-normalized AUC of quetiapine versus age on combined data from children and adults

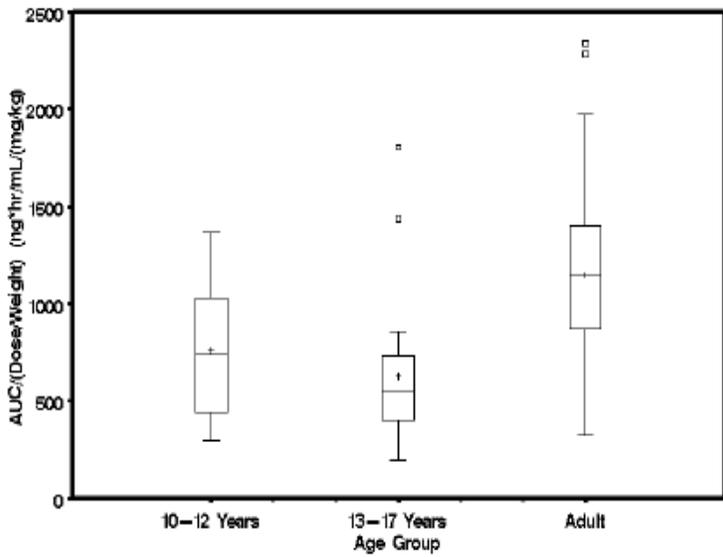
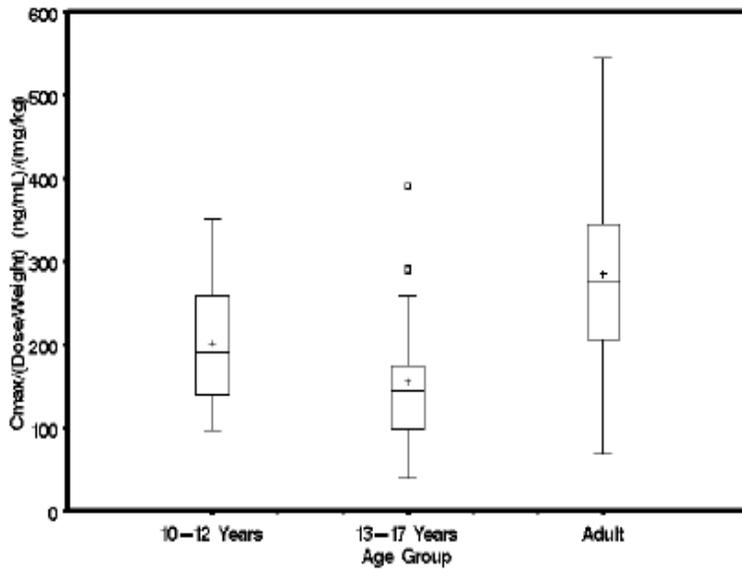


Figure 3: Box plot of Dose-normalized, weight-normalized  $C_{max}$  of quetiapine versus age on combined data from children and adults



*Does quetiapine prolong QTc interval in children and adolescents at the proposed clinical doses?*

Quetiapine does not appear to prolong QTc interval in children and adolescents at the proposed clinical doses. The potential for QTc prolongation at the proposed doses was evaluated by using the quetiapine concentration-QTcF relationship derived from a thorough QT study in healthy adults. Assuming the concentration-QT relationships are similar between the pediatric patients and healthy adults, the model predicted mean placebo-corrected, baseline-adjusted QTc ( $\Delta\Delta QTc$ ) intervals are less than 10 ms following the highest dose (i.e. 400 mg BID) tested in the two pivotal pediatric studies (Study D1441C00112 and Study D1441C00149). In addition, the largest observed mean QTc interval change from baseline ( $\Delta QTcF$ ) observed in the clinical trials was around 2 ms. No patients had QTcF values larger than 500 ms or  $\Delta QTcF$  greater than 60 ms.

Table 3: Model Predicted  $\Delta\Delta QTcF$  Values

Daily Dose (mg/day)	Dose (mg)	Dosing	$C_{max}$ (ng/mL)	Predicted QTcF (90% CI) (ms)
400	200	BID	520.9	5.4 (3.6 - 7.1)
600	300	BID	1023.6	6.8 (4.9 - 8.7)
800	400	BID	1113.4	6.9 (5.0 - 8.9)

## 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?*

The sponsor submitted this supplemental New Drug Application (sNDA) for Seroquel® (quetiapine fumarate) Tablets for Pediatric Exclusivity determination in response to a Pediatric Written Request issued by the Agency. The supplement contains, pharmacokinetic, efficacy and safety data for the use of Seroquel in the treatment of schizophrenia and bipolar mania in pediatric patients. No new information was included in the CMC (chemistry, manufacturing, and control), biopharmaceutics or preclinical, sections of this sNDA. These sections are cross-referenced to NDA 20-639 and associated supplements. The purpose of the clinical pharmacology evaluation was to characterize the steady-state pharmacokinetics (PK) of Seroquel™, administered twice daily as quetiapine immediate-release tablets (up to total daily doses of 800 mg) in children and adolescents 10 to 17 years of age with diagnoses of bipolar I or schizoaffective disorder.

Quetiapine is a dibenzothiazepine derivative marketed in the US and a number of other countries for the treatment of adult patients with schizophrenia and bipolar disorder, including bipolar depression, bipolar mania and bipolar maintenance. The recommended dose range of quetiapine in adults is between 150 mg and 750 mg; safety data are available for doses up to 800 mg per day.

The sponsor conducted a study to characterize the steady-state pharmacokinetics (PK) of quetiapine administered as quetiapine tablets in children and adolescents 10 to 17 years of age with schizoaffective or bipolar I disorder. This study was conducted in response to a Pediatric Written Request issued by the Agency for information on quetiapine in subjects aged 10 to 17 years. The PK results in this pediatric study was compared to a study (Study D1441C00130) in adults (18 to 45 years) to determine if there are differences in the exposure between the pediatric and adult patients. The overall objective and design of the two studies (Studies D1441C00028 and D1441C00130) were similar.

### *2.2 General Clinical Pharmacology*

#### *2.2.1 What is the proposed therapeutic indication for quetiapine IR in this submission?*

This sNDA seeks approval of the use of Seroquel® (quetiapine fumarate) in treatment of schizophrenia and bipolar mania in pediatric patients

#### *2.2.2 What are the proposed dosing recommendations for Seroquel in pediatric patients?*

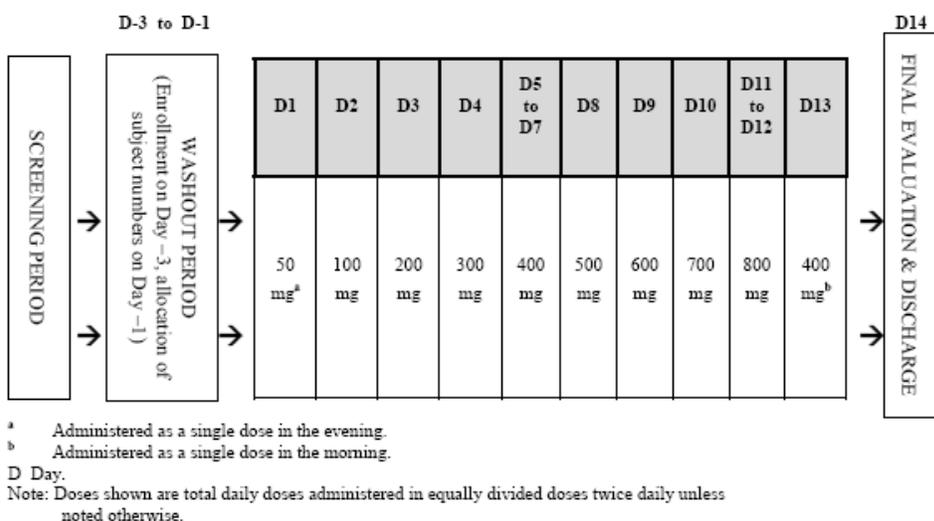
The total daily dose for the initial five days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4) and 400 mg (Day 5). After Day 5, the dose should be adjusted within the recommended dose range of 400 to 600 mg for mania and 400 to 800 mg/day for schizophrenia based on response and tolerability. Dose adjustments should be in increments of no greater than 100 mg/day.

2.2.3 What is the Pharmacokinetics of Quetiapine and its Metabolites in Pediatric patients aged 10 – 17 years?

Exposure to quetiapine in terms of AUC<sub>0-∞</sub> and C<sub>ss,max</sub> appeared to be higher in the 10- to 12-year-old subjects than in the 13- to 17-year-old subjects on Days 7 and 13. The geometric means for AUC<sub>0-∞</sub> on Days 7 and 13 were 55% and 36% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 – 17 year old. The geometric means for C<sub>ss,max</sub> on Days 7 and 13 were 71% and 54% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 -17 year olds.

The study in pediatric patients was a multicenter, open-label, inpatient, steady-state, PK, safety and tolerability study in children and adolescents (10 to 17 years) with confirmed clinical diagnoses of schizophrenia, schizoaffective disorder or bipolar disease. Subjects received ascending total daily doses of quetiapine, administered in equally divided doses twice daily unless noted otherwise. Plasma and urine concentrations of quetiapine and its metabolites were measured after the morning doses were administered on Day 7 (200-mg dose) and Day 13 (400- mg dose). Safety was assessed by recording adverse events (AEs) and collecting vital signs measurements, electrocardiographic (ECG) data and clinical laboratory tests. The following figure depicts the design of the study.

Figure 4: Flow chart depicting the design of study in pediatric patients



Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 7 and Day 13 for subjects who received the 200 and 400 mg morning dose are provided in the following figures

Figure 5: Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 7 for subjects who received the 200 mg morning dose

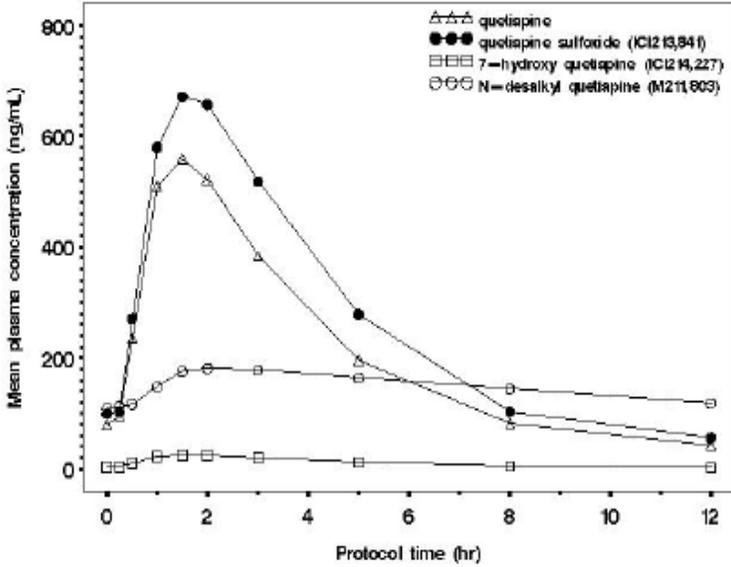


Figure 6: Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 13 for subjects who received the 400 mg morning dose

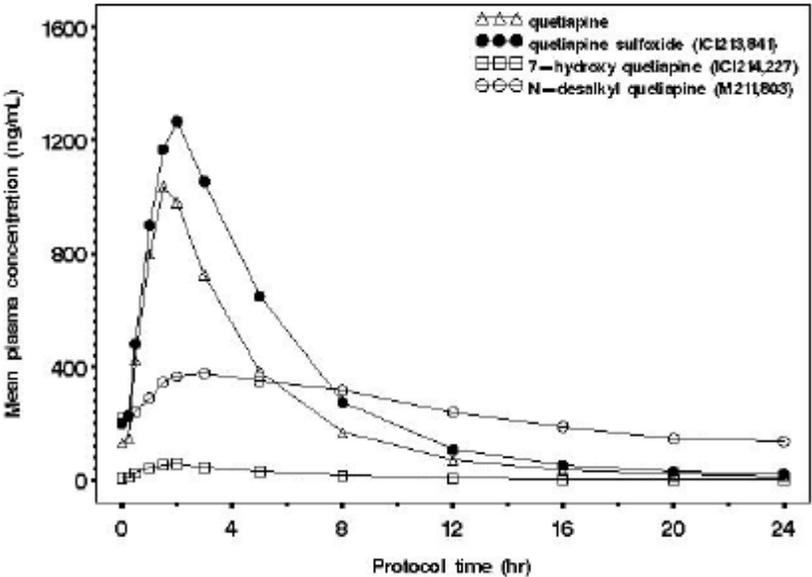
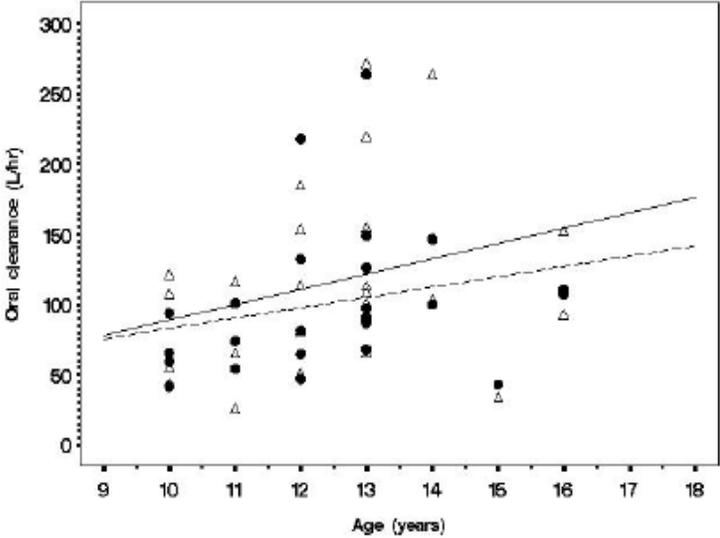
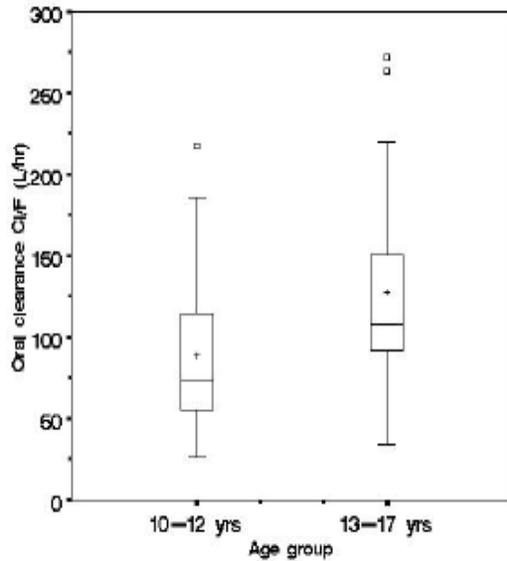


Figure 7: Scatter plot of oral clearance of quetiapine by age for Day 7 and Day 13



Triangle: Observed values for Day 7  
Dot: Observed values for Day 13  
Solid line: Linear regression for Day 7  
Dash line: Linear regression for Day 13

Figure 8: Box plots of oral clearance of quetiapine on Day 7 and Day 13 by age group



Note: The horizontal lines in the graph indicate the 10th,25th,50th,75th,and 90th percentiles

Pharmacokinetic parameters for quetiapine are presented in the following table. Exposure to quetiapine in terms of AUC<sub>0-∞</sub> and C<sub>ss,max</sub> appeared to be higher in the 10- to 12-year-old subjects than in the 13- to 17-year-old subjects on Days 7 and 13. The geometric means for AUC<sub>0-∞</sub> on Days 7 and 13 were 55% and 36% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 – 17 year old. The geometric means for C<sub>ss,max</sub> on Days 7 and 13 were 71% and 54% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 -17 year olds. The quetiapine C<sub>ss,min</sub> was 22% and 21% higher for the 10- to 12-year-old subjects on Days 7 and 13, respectively as compared to the 13 to 17 year olds. The apparent oral clearance (CL/F) was 38% and 30% lower for the 10- to 12-year-old subjects on Days 7 and 13, respectively as compared to 13 to 17 year olds.

Table 4: Mean Pharmacokinetic parameters for quetiapine by age group

PK parameter	Statistic	Age group					
		10-12 yrs (n=9) <sup>a</sup>		13-17 yrs (n=12)		Total (n=21) <sup>a</sup>	
		Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC <sub>ss</sub> (ng*hr/mL)	Geometric mean	2560.0	5145.0	1651.4	3784.8	1992.8	4317.1
	CV (%)	56.8	29.1	64.5	46.6	65.0	42.4
C <sub>ss,max</sub> (ng/mL)	Geometric mean	707.0	1426.3	414.3	924.7	520.9	1113.4
	CV (%)	37.5	33.9	69.4	51.6	63.9	49.8
t <sub>max</sub> (hr)	Median	1.08	1.50	1.57	1.50	1.50	1.50
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Maximum	2.00	2.00	3.00	2.00	3.00	2.00
C <sub>ss,min</sub> (ng/mL)	Geometric mean	33.1	66.7	27.2	54.9	29.6	59.7
	CV (%)	113.5	74.4	99.9	66.9	102.9	69.0
CL/F (L/hr)	Mean	87.1	80.7	140.1	115.8	117.4	100.8
	SD	39.0	24.8	75.6	55.4	66.9	47.4
t <sub>1/2</sub> (hr)	Mean	3.17	5.52	2.77 <sup>b</sup>	5.52 <sup>b</sup>	2.96 <sup>c</sup>	5.52 <sup>c</sup>
	SD	0.99	1.38	0.56	0.77	0.80	1.07
Ael <sub>(m)</sub> (μg)	Mean	143.7	281.9	101.8	253.0	119.8	265.4
	SD	145.3	217.2	50.5	99.4	101.5	156.6
Fu (%)	Mean	0.072	0.070	0.051	0.063	0.060	0.066
	SD	0.073	0.054	0.025	0.025	0.051	0.039
CL <sub>R</sub> (L/hr)	Mean	0.063	0.053	0.070	0.077	0.067	0.067
	SD	0.083	0.036	0.052	0.058	0.065	0.050

<sup>a</sup> Number of subjects who received 400-mg morning dose on Day 13.

<sup>b</sup> Excludes 2 of 12 subjects for whom t<sub>1/2</sub> could not be calculated.

<sup>c</sup> Excludes 2 of 21 subjects for whom t<sub>1/2</sub> could not be calculated.

Ael<sub>(m)</sub> amount of metabolite eliminated. AUC<sub>ss</sub> area under the curve at steady-state. CL/F apparent oral clearance. CV coefficient of variation. CL<sub>R</sub> renal clearance from plasma. C<sub>ss,max</sub> maximum plasma concentration at steady-state. C<sub>ss,min</sub> minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t<sub>max</sub> time of maximum plasma concentration. t<sub>1/2</sub> terminal elimination half-life.

The pharmacokinetic parameters of the active metabolite, N-desalkyl quetiapine is provided in the following table.

Table 5: Pharmacokinetic parameters for N-desalkyl quetiapine for subjects who received the 200 mg and 400 mg morning dose

PK parameter <sup>b</sup>	Statistic	Age group					
		10-12 yrs (n=9) <sup>a</sup>		13-17 yrs (n=12)		Total (n=21) <sup>a</sup>	
		Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC <sub>0-∞</sub> (ng*hr/mL)	Geometric mean	1977.4	4074.0	1497.1	3380.7	1686.7	3662.1
	CV (%)	13.7	20.6	34.1	33.3	30.3	29.5
C <sub>ss,max</sub> (ng/mL)	Geometric mean	214.9	460.3	164.7	347.7	184.6	392.1
	CV (%)	18.8	23.4	33.8	36.5	31.0	34.2
t <sub>max</sub> (hr)	Median	2.00	2.00	3.00	3.00	3.00	3.00
	Minimum	1.00	1.50	1.00	1.50	1.00	1.50
	Maximum	12.00	8.00	8.00	8.00	12.00	8.00
C <sub>ss,min</sub> (ng/mL)	Geometric mean	126.9	250.4	100.2	223.5	110.8	234.7
	CV (%)	20.0	22.1	34.3	25.3	30.9	24.1
Ael <sub>(ex)</sub> (μg)	Mean	2231.1	5069.6	2328.3	5806.0	2286.7	5490.4
	SD	1813.9	3131.1	1776.0	4021.5	1747.4	3599.4
Fu (%)	Mean	1.448	1.645	1.511	1.884	1.484	1.782
	SD	1.178	1.016	1.153	1.305	1.134	1.168
CL <sub>R</sub> (L/hr)	Mean	1.052	1.210	1.610	1.755	1.371	1.521
	SD	0.776	0.704	1.514	1.466	1.258	1.207

<sup>a</sup> Number of subjects who received 400-mg morning dose on Day 13.

<sup>b</sup> t<sub>1/2</sub> results are omitted from this table as there were only 5 subjects who provided data on both Days 7 and 13.

Ael<sub>(ex)</sub> amount of metabolite eliminated. AUC<sub>0-∞</sub> area under the curve at steady-state. CL<sub>R</sub> renal clearance from plasma.

C<sub>ss,max</sub> maximum plasma concentration at steady-state. C<sub>ss,min</sub> minimum plasma concentration at steady-state.

Fu mole fraction (percent) of dose excreted in the urine. NA not applicable. SD standard deviation.

t<sub>max</sub> time of maximum plasma concentration. t<sub>1/2</sub> terminal elimination half-life.

The means for AUCss for N-desalkyl quetiapine on Days 7 and 13 were 32% and 21% higher, respectively, for the 10- to 12-year-old subjects compared to 13 to 17 year olds. The means for C<sub>ss,max</sub> on Days 7 and 13 were 30% and 32% higher, respectively, for 10- to 12-year-old subjects compared to the 13 to 17 year old.

In terms of in vivo exposure, the rank order of exposure with respect to both AUCss and C<sub>ss,max</sub> was: quetiapine sulfoxide>quetiapine> N-desalkyl quetiapine>7-hydroxy quetiapine. Quetiapine sulfoxide and 7-hydroxy quetiapine are inactive metabolites.

### 2.2.4 How does the exposure to quetiapine in pediatric patients compare to adults?

The comparison of pharmacokinetics between pediatric patients and adults was done across two studies. The study designs for the two studies were similar.

#### 2.2.4.1 Dose normalized exposure comparison

Comparison of dose normalized exposures (AUC<sub>ss</sub> and C<sub>max</sub>) to quetiapine showed a 12% decrease in AUC and 8% decrease in C<sub>max</sub> in pediatric children ages 10 to 17 years old compared to adults (ages 18 to 45 years).

Dose normalized AUC increased by about 6% and C<sub>max</sub> increased by 16% when children 10 – 12 years are compared to adults. But when children 13 – 17 years are compared to adults, dose normalized AUC and C<sub>max</sub> decreased by about 27% and 28% respectively.

Table 6: Comparison of dose-normalized exposure (AUC<sub>ss</sub> and C<sub>max</sub>) to quetiapine and 3 metabolites in children/adolescents with exposure in adults

Analyte	Dose-normalized AUC <sub>ss</sub>		Dose-normalized C <sub>ss,max</sub>	
	Mean ratio <sup>a</sup>	90% CI	Mean ratio <sup>a</sup>	90% CI
Quetiapine	0.88	0.76, 1.03	0.92	0.79, 1.06
Quetiapine sulfoxide	1.27	1.15, 1.39	1.30	1.16, 1.44
7-hydroxy quetiapine	1.08	0.92, 1.26	1.11	0.94, 1.31
N-desalkyl quetiapine	1.45	1.30, 1.61	1.31	1.15, 1.49

<sup>a</sup> Ratio (10- to 17-year-olds:adults) of least squares means from ANOVA model.

ANOVA analysis of variance. AUC<sub>ss</sub> area under the curve at steady-state. CI confidence interval. C<sub>ss,max</sub> maximum plasma concentration at steady-state.

Table 7: Comparison of dose-normalized AUC and C<sub>max</sub> of quetiapine and 3 metabolites in children (10 -12 years) with exposure in adults (18 – 45 years)

Analyte	Dose- Normalized AUC		Dose –Normalized C <sub>max</sub>	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	1.06	0.88 – 1.26	1.16	0.99 – 1.35
Quetiapine sulfoxide	1.43	1.29 – 1.58	1.53	1.37 – 1.72
7-hydroxy quetiapine	1.16	0.97 – 1.40	1.23	1.00– 1.51
N-desalkyl quetiapine	1.63	1.44 – 1.84	1.49	1.26 – 1.75

Post hoc analyses with no control for multiplicity.

Table 8: Comparison of dose-normalized AUC and Cmax of quetiapine and N-desalkyl quetiapine in adolescents (13 - 17 years) with exposures in adults (18 – 45 years)

Analyte	Dose- Weight Normalized AUC		Dose –Weight normalized Cmax	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	0.73	0.61 – 0.88	0.72	0.60 – 0.86
Quetiapine sulfoxide	1.11	0.99 – 1.25	1.06	0.94 – 1.21
7-hydroxy quetiapine	1.00	0.81 – 1.22	0.98	0.78 – 1.22
N-desalkyl quetiapine	1.28	1.12 – 1.47	1.14	0.96 – 1.35

Post hoc analyses with no control for multiplicity.

The following figures provide a comparison of the pediatric populations to adults in an across studies comparison.

Figure 9: Box plot of Dose-normalized AUC of quetiapine versus age on combined data from children and adults

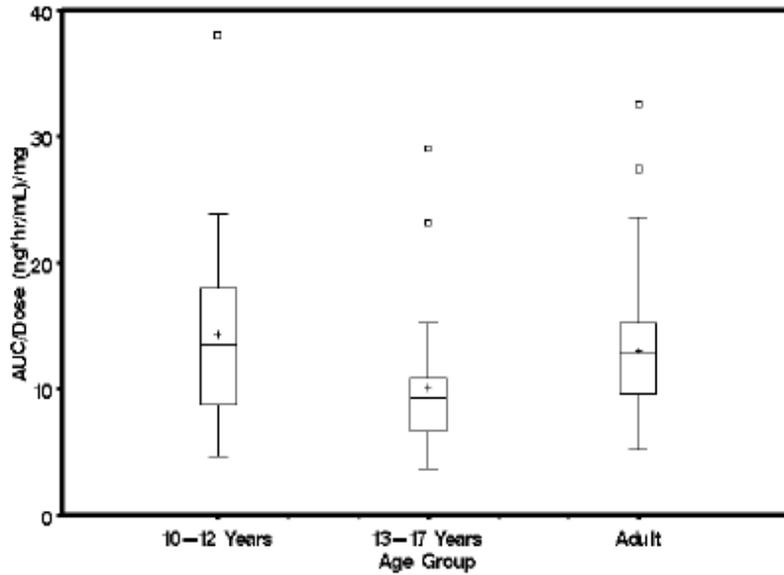
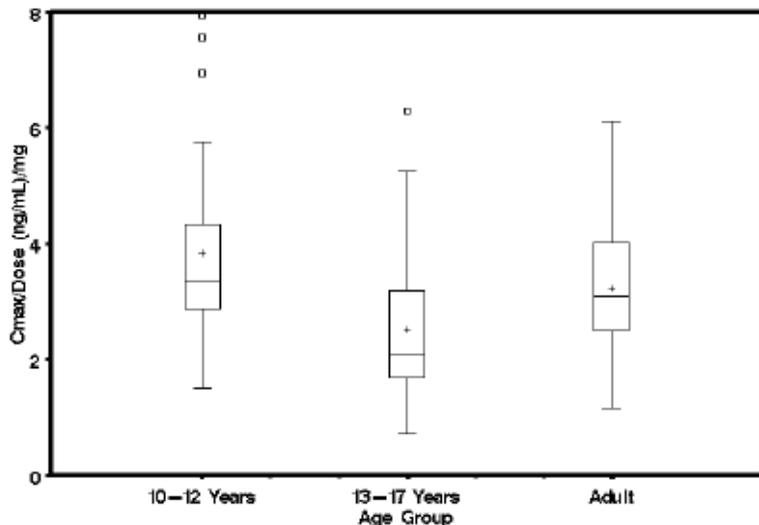


Figure 10: Box plot of Dose-normalized Cmax of quetiapine versus age on combined data from children and adults



#### 2.2.4.2 Dose normalized, weight normalized exposure comparison

Dose normalized, weight-normalized AUC decreased by 41% and Cmax decreased by 39% when pediatric children ages 10 to 17 were compared to adults. The decrease in exposure may not be clinically relevant.

Dose normalized, weight normalized AUC decreased by about 35% and Cmax decreased by 28% when children 10 – 12 years are compared to adults. When children 13 – 17 years are compared to adults, dose normalized, weight-normalized AUC and Cmax decreased by about 47% and 48% respectively. These decreases in exposure are not expected to be clinically relevant.

The following tables provide a comparison of the pediatric populations to adults in an across studies comparison.

Table 9: Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites in children/adolescents with exposures in adults

Analyte	Dose- Weight Normalized AUC		Dose –Weight normalized Cmax	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	0.59	0.50 – 0.70	0.61	0.53 – 0.72
Quetiapine sulfoxide	0.85	0.77 – 0.93	0.86	0.79 – 0.95
7-hydroxy quetiapine	0.72	0.61 – 0.84	0.74	0.63 – 0.87
N-desalkyl quetiapine	0.96	0.86 – 1.07	0.87	0.76 – 1.00

Post hoc analyses with no control for multiplicity.

Table 10: Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites in children, 10 – 12 years with exposures in adults

Analyte	Dose- Weight Normalized AUC		Dose –Weight normalized Cmax	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	0.65	0.53 – 0.80	0.72	0.60 – 0.85
Quetiapine sulfoxide	0.89	0.79 – 1.00	0.95	0.85 – 1.06
7-hydroxy quetiapine	0.72	0.59 – 0.88	0.76	0.62 – 0.94
N-desalkyl quetiapine	1.00	0.87 – 1.16	0.92	0.78 – 1.10

Post hoc analyses with no control for multiplicity.

Table 11: Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites in adolescents, 13 - 17 years with exposures in adults

Analyte	Dose- Weight Normalized AUC		Dose –Weight normalized Cmax	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	0.53	0.43 – 0.65	0.52	0.43 – 0.63
Quetiapine sulfoxide	0.81	0.71 – 0.91	0.77	0.68 – 0.87
7-hydroxy quetiapine	0.72	0.59 – 0.89	0.71	0.57 – 0.88
N-desalkyl quetiapine	0.92	0.80 – 1.07	0.82	0.69 – 0.98

Post hoc analyses with no control for multiplicity.

Figure 13: Box plot of Dose-normalized, weight normalized AUC of quetiapine versus age on data from children versus adults

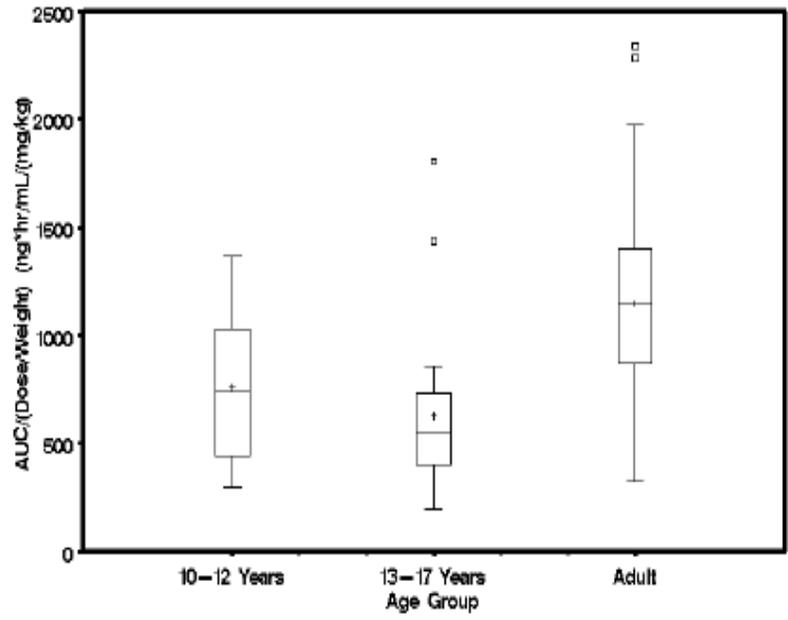


Figure 14: Box plot of Dose-normalized, weight-normalized C<sub>max</sub> of quetiapine versus age on children and adults

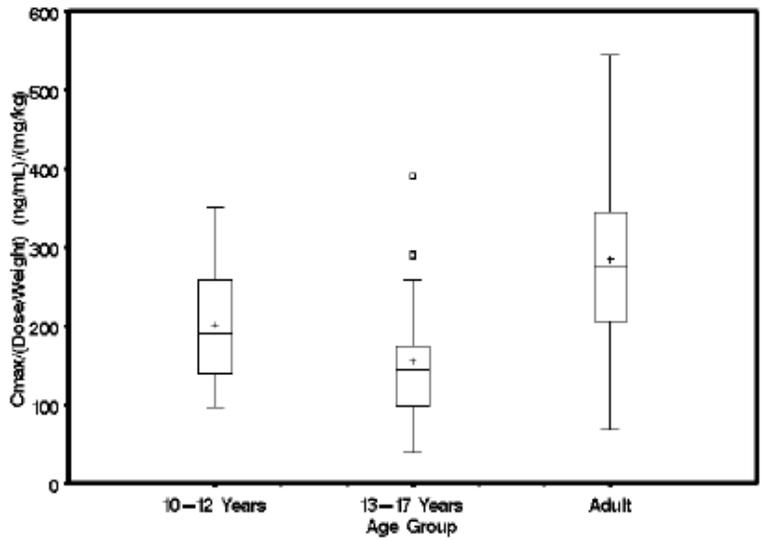


Figure 15: Box plot of Dose-normalized, weight-normalized C<sub>min</sub> of quetiapine versus age of data from children and adults

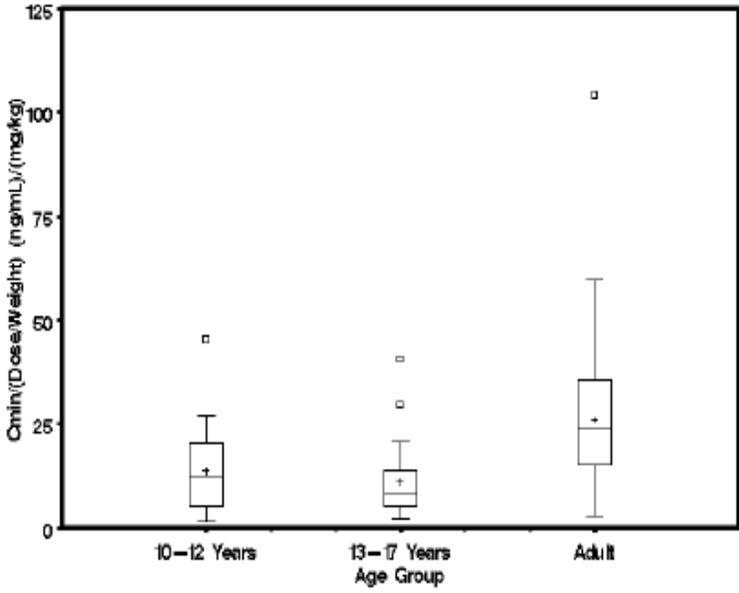
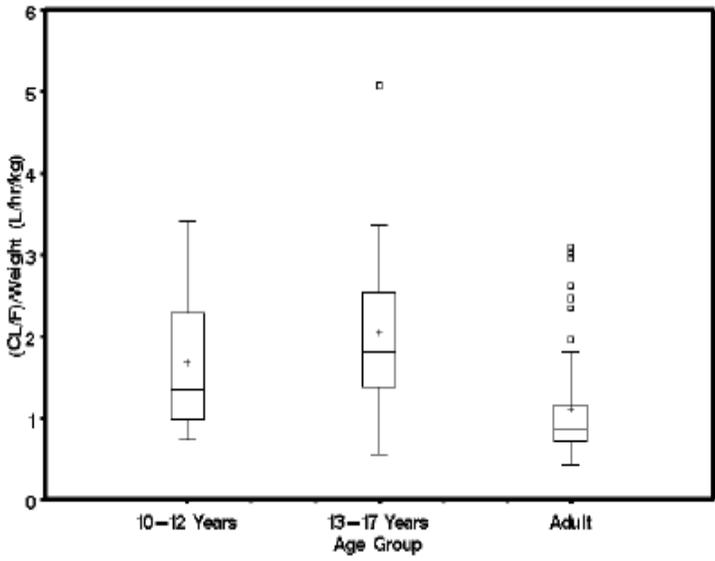


Fig 16: Box plot of Weight-normalized Oral Clearance (Cl/F) of quetiapine versus age on combined data from children and adults



Comparisons of weight-adjusted, dose normalized exposure showed evidence of significant age-related differences in exposure to quetiapine, with about 41% lower exposures seen in children/adolescents. These comparisons of weight-adjusted, dose-normalized exposure showed no evidence for age-related differences in exposure to N-desalkyl quetiapine metabolites. The differences in exposures between the pediatric patients and adults may not be clinically relevant.

*2.2.5. Does quetiapine prolong QTc interval in children and adolescents at the proposed clinical doses?*

Quetiapine does not appear to prolong QTc interval in children and adolescents at the proposed clinical doses. The potential for QTc prolongation at the proposed doses was evaluated by using the quetiapine concentration-QTcF relationship derived from a thorough QT study in healthy adults. Assuming the concentration-QT relationships are similar between the pediatric patients and healthy adults, the model predicted mean placebo-corrected, baseline-adjusted QTc ( $\Delta\Delta\text{QTc}$ ) intervals are less than 10 ms (Table 12) following the highest dose (i.e. 400 mg BID) tested in the two pivotal pediatric studies (Study D1441C00112 and Study D1441C00149). In addition, the largest observed mean QTc interval change from baseline ( $\Delta\text{QTcF}$ ) observed in the clinical trials was around 2 ms (Table 13). No patients had QTcF values larger than 500 ms or  $\Delta\text{QTcF}$  greater than 60 ms.

Table 12: Model Predicted  $\Delta\Delta\text{QTcF}$  Values

Daily Dose (mg/day)	Dose (mg)	Dosing	C <sub>max</sub> (ng/mL)	Predicted QTcF (90% CI) (ms)
400	200	BID	520.9	5.4 (3.6 - 7.1)
600	300	BID	1023.6	6.8 (4.9 - 8.7)
800	400	BID	1113.4	6.9 (5.0 - 8.9)

Table 13: Summary of the QTcF change from Baseline Values

Study		D1441C00112	D1441C00149
Patients		schizophrenia	Bipolar I mania
Treatment	Age	13 ~ 17	10 ~ 17
Placebo	Mean (SD)	-2.1 (18.1)	-1.2 (17.6)
	N	71	81
	400 mg/day	Mean (SD)	1.96 (16.2)
600 mg/day	N	72	94
	Mean (SD)	-	-1.1 (16.8)
	N	-	98
800 mg/day	Mean (SD)	1.96 (18.1)	-
	N	73	-

*2.2.6. What were overall adverse events profile in Study 28 reported by the sponsor?*

In this pharmacokinetic study, the sponsor reported that quetiapine was well tolerated in this subject population and no new safety concerns were identified. There were no deaths or serious AEs during or after treatment. There were no apparent differences between younger and older subjects' safety profiles. Somnolence was the most frequently occurring adverse event during treatment. The majority of cases were considered treatment related, were rated as mild in intensity by the investigator, and were transient. A comparison of the occurrence of AEs in children and adolescents in the present study with AE occurrence in adults in Study D1441C00130 showed adult subjects reported 1 or more AEs more frequently than children. Dizziness was reported more frequently in adults than in children and adolescents. The sponsor stated that there were no other obvious differences between children and adults in the types or severity of AEs reported; however, the small sample sizes in both studies limit the comparisons that can be made between the safety profiles. The sponsor reported that increases in mean ALT and mean heart rates were seen in children and adolescents in the present study; however these changes were not unexpected and were not clinically meaningful. No other trends were seen in other clinical laboratory tests, vital signs measurements or ECG parameters.

**3. Detailed Labeling Recommendations**

Detailed OCP Labeling recommendations are incorporated in the proposed label attached under Appendices. The following recommended revisions is to the paragraph under "Children and Adolescents" under section 12.3. The proposed label is provided in the Appendix.

**Children and Adolescents**



#### **4. Appendix**

Proposed Label with OCP recommendations. OCP edits are noted as “Track Changes: in the proposed label

Clinical Pharmacology Individual Reports

Pharmacometric Review

55 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## 4.2 Individual Reports

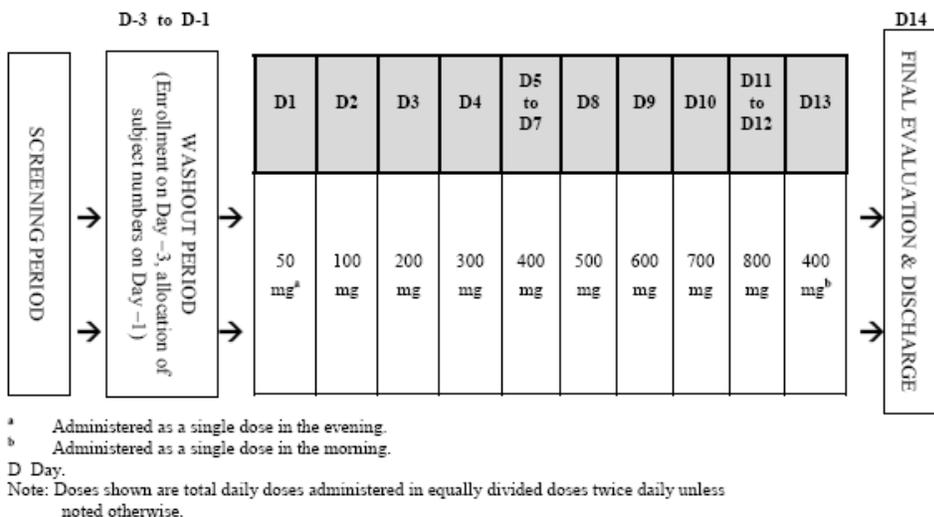
**Title (Protocol D1441C00028):** A Study to Characterize the Steady-State Pharmacokinetics, Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) in Children and Adolescents with Selected Psychotic Disorders

**Objectives:** To characterize the steady-state pharmacokinetics (PK) of quetiapine fumarate (SEROQUEL™, quetiapine) administered as quetiapine tablets in children and adolescents 10 to 17 years of age. The secondary objectives were:

1. To monitor the tolerability and safety of titrating doses of quetiapine
2. To determine the dose-proportionality for quetiapine
3. Compare the AUC and C<sub>max</sub> between the subjects in this trial and D1441C00130
4. To characterize the PK of 3 metabolites: quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine

**Study Design:** This was a multicenter, open-label, inpatient, steady-state, PK, safety and tolerability study in children and adolescents (10 to 17 years) with confirmed clinical diagnoses of schizophrenia, schizoaffective disorder or bipolar disease. Subjects received ascending total daily doses of quetiapine, administered in equally divided doses twice daily unless noted otherwise, as follows: Day 1 (a single 50-mg dose in the evening), Day 2 (100 mg), Day 3 (200 mg), Day 4 (300 mg), Days 5 to 7 (400 mg), Day 8 (500 mg), Day 9 (600 mg), Day 10 (700 mg), Days 11 and 12 (800 mg), and Day 13 (a single 400-mg dose in the morning). Plasma and urine concentrations of quetiapine and its metabolites were measured after the morning doses were administered on Day 7 (200-mg dose) and Day 13 (400-mg dose). The study used intact quetiapine 25-mg tablets (formulation number F12804; batch number 2000058452; lot number 7527F) and 100-mg tablets (formulation number F12689; batch number 2000058452; lot number 7511H) that were administered orally, every 12 hours. Safety was assessed by recording adverse events (AEs) and collecting vital signs measurements, electrocardiographic (ECG) data and clinical laboratory tests.

The following figure is a flow chart depicting the design of the study.



Multiple blood samples for determining plasma concentrations were drawn as follows:

- On Day 7 immediately prior to the 200-mg morning dose (time 0) and 0.25, 0.5, 1, 1.5, 2, 3, 5, 8 and 12 hours after this dose
- On Day 13 immediately prior to the 400-mg morning dose (time 0) and at 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 20, and 24 hours after this dose

To verify that steady-state was achieved, pre-dose blood samples were obtained as follows:

- On Days 6 and 7 prior to the 200-mg morning dose
- On Day 7 12 hours after dosing
- On Days 12 and 13 prior to the 400-mg morning dose
- On Day 13 12 hours after the 400-mg morning dose

Subjects were not permitted to take any concurrent antipsychotic or psychotropic medications, with the exception of valproic acid and lithium. Subjects who were stabilized on either of these medications for at least 1 month prior to the first administration of study treatment were permitted to continue these treatments at their current dose. All other antipsychotic and psychotropic medications were to be discontinued for at least 3 days before beginning study treatment. Acetaminophen was the only medication allowed for analgesia without prior consultation with the sponsor. Oral lorazepam was permitted for acute agitation or severe insomnia, with the dosage determined at the discretion of the principal investigator.

**Analytical Methods:** The concentrations of quetiapine, quetiapine sulfoxide (M213,841), 7-hydroxy quetiapine (M214,227), and N-desalkyl quetiapine (M211,803) in plasma and urine were determined using a validated reverse-phase liquid chromatography and turbo ionspray ionization tandem mass spectrometry (LC/MS/MS). The method has a validated assay range of 0.500 to 500 ng/mL for all analytes, utilizing a 100 µL sample aliquot with extension of the validated curve range to 10.0 µg/mL (50 µg/mL for urine) with appropriate dilution.

**Data Analysis:** The following pharmacokinetic parameters were computerized by non-compartmental methods: Blood samples: AUC<sub>ss</sub>, C<sub>ss,max</sub>, C<sub>ss,min</sub>, T<sub>1/2</sub>, T<sub>max</sub>, CL/F, F<sub>u</sub>, Ael(m), CLR, and λ<sub>z</sub> for quetiapine and AUC<sub>ss</sub>, C<sub>ss,max</sub>, C<sub>ss,min</sub>, t<sub>1/2</sub>, t<sub>max</sub>, F<sub>u</sub>, Ael(m), CLR, and λ<sub>z</sub> for 3 metabolites (quetiapine sulfoxide, 7-hydroxy quetiapine, and N-desalkyl quetiapine). AUC<sub>ss</sub> and C<sub>ss,max</sub> following the 200-mg and 400-mg morning doses on Days 7 and 13 were the primary variables. Urine samples: F<sub>u</sub> and Ael(m) for quetiapine 4 metabolites (quetiapine sulfoxide, 7-hydroxy quetiapine, N-desalkyl quetiapine and 7-hydroxy N-desalkyl quetiapine).

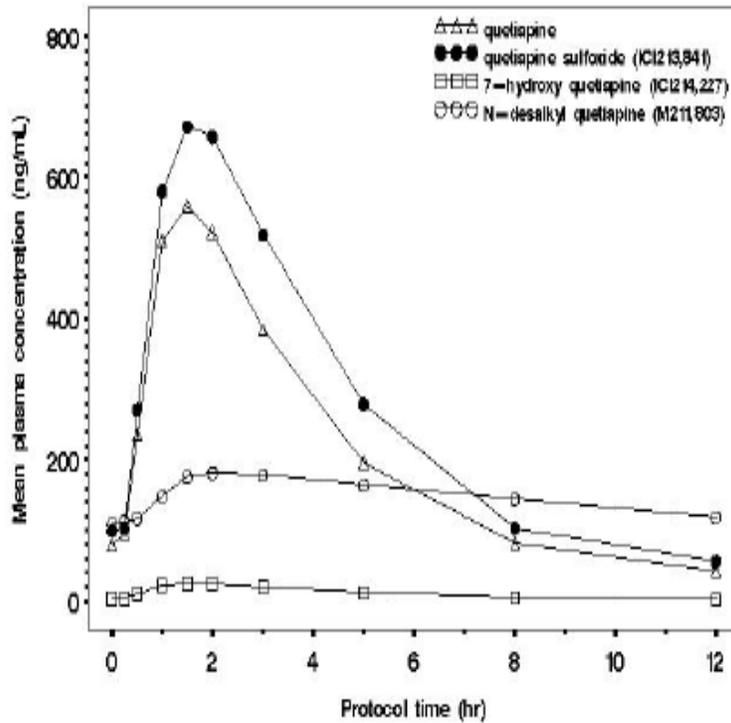
Plasma concentrations and PK parameters for quetiapine and its metabolites were summarized descriptively for each dose for all subjects and by age group (10-12 years and 13-17 years). To assess the dose-proportionality of quetiapine, log-transformed AUC<sub>ss</sub> and C<sub>ss,max</sub> for the 400-mg morning dose were compared to the log-transformed AUC<sub>ss</sub> and C<sub>ss,max</sub> for the 200-mg morning dose, respectively, using analysis of variance (ANOVA) methods. Comparisons of exposure in children/adolescents with that in adults (from Study D1441C00130) used the following models: log-transformed, dose-normalized AUC<sub>ss</sub> and C<sub>ss,max</sub> were analyzed separately using ANOVA with a term for age group (ie, 10- to 17-year-old subjects or adult subjects). Least squares means and 90% confidence intervals for the ratios of interest (ie, AUC<sub>ss</sub> for 10- to 17-year-olds: AUC<sub>ss</sub> for adults and C<sub>ss,max</sub> for 10- to 17-year-olds:C<sub>ss,max</sub> for adults) were calculated. If the 90% confidence intervals for both AUC<sub>ss</sub> and C<sub>ss,max</sub> were completely contained within the interval 0.71 to 1.41, it was concluded that there was no difference in exposure between adults and 10- to 17-year-old subjects.

**Results:** Twenty-eight subjects were enrolled in this study. Twenty-seven of the 28 subjects received the study medication; 1 subject was withdrawn from the study after enrollment but prior to receiving study medication. As a result, 27 subjects were included in the safety population. Three additional subjects withdrew from the study prior to completion; therefore, 24 subjects were evaluable for PK analyses. Three subjects in the 10- to 12-year age group were unable to tolerate daily doses above 600 mg and remained on 600 mg per day from Day 11 onward, as allowed by the protocol. Of the 27 subjects in the safety population, 13 were in the 10- to 12-year age range, and 14 were in the 13- to 17-year age range. The median age of subjects in the safety population was 13 years. In the 13- to 17-year-old age group, 10 of the 14 subjects were 13 or 14 years old. Approximately one-half of the subjects in each age group were male. Approximately one-half of all subjects were black; the proportion of blacks was slightly higher in the 13- to 17-year-old age group. All but 1 of the subjects had a diagnosis of bipolar I disorder; 1 subject in the 10- to 12-year-old age group had a diagnosis of schizoaffective disorder.

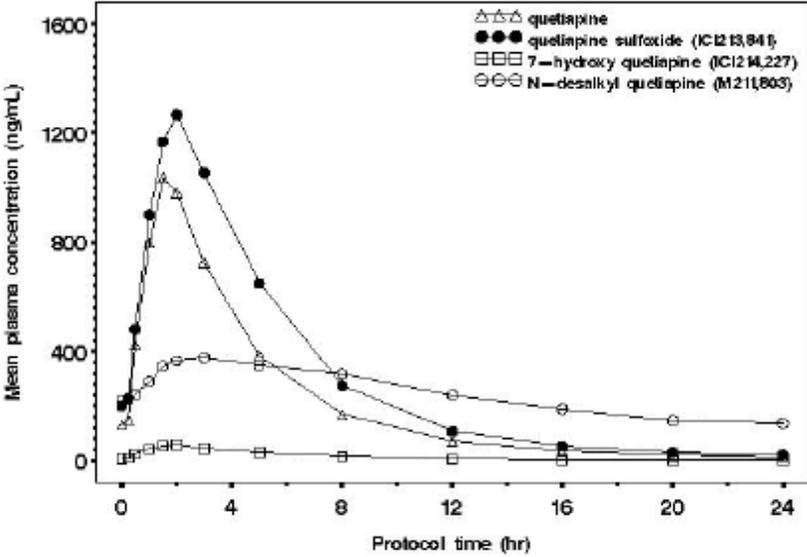
## Pharmacokinetic Results

Mean plasma concentrations over time for quetiapine and 3 metabolites on Days 7 and 13.

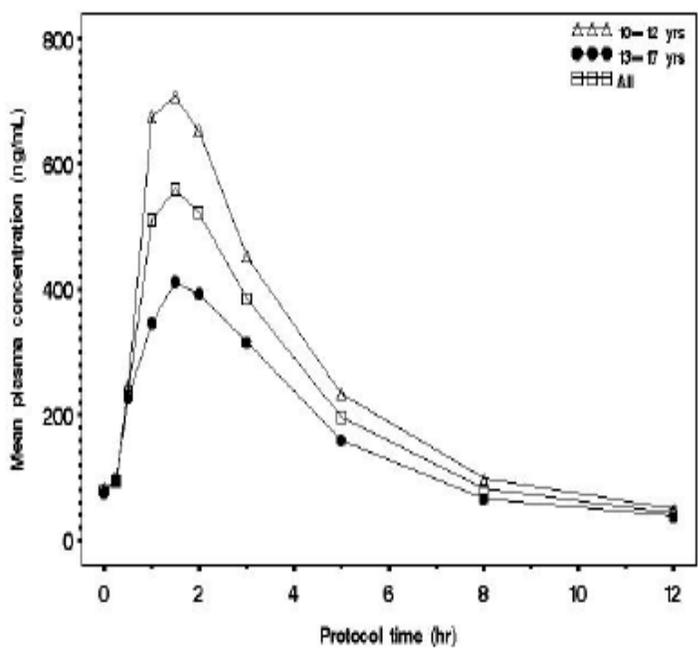
Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 7 for subjects who received the 200 mg morning dose



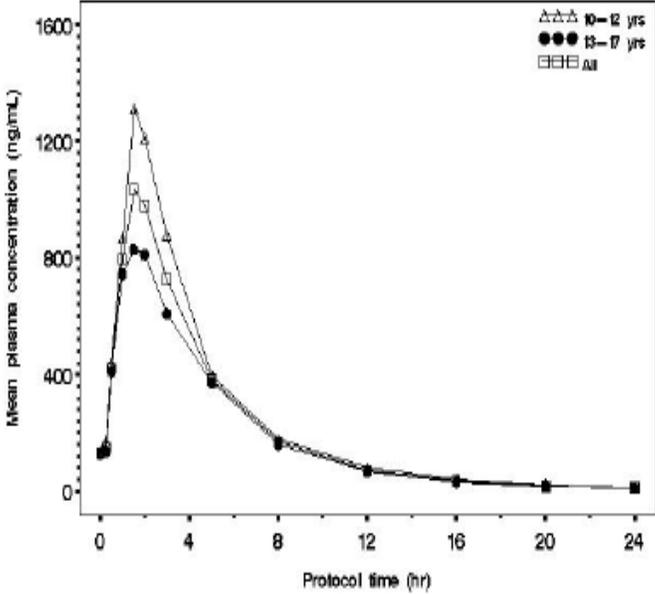
Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 13 for subjects who received the 400 mg morning dose



Mean plasma concentrations of quetiapine over time in Day 7 for PK population subjects who received the 200 mg morning dose



Mean plasma concentrations of quetiapine over time on Day 13 for PK population subjects who received the 400 mg morning dose



Descriptive statistics of the pharmacokinetic parameters for quetiapine are presented in the following table.

Pharmacokinetic parameters for quetiapine for subjects who received the 200 and 400-mg morning dose

PK parameter	Statistic	Age group					
		10-12 yrs (n=9) <sup>a</sup>		13-17 yrs (n=12)		Total (n=21) <sup>a</sup>	
		Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC <sub>ss</sub> (ng*hr/mL)	Geometric mean	2560.0	5145.0	1651.4	3784.8	1992.8	4317.1
	CV (%)	56.8	29.1	64.5	46.6	65.0	42.4
C <sub>ss,max</sub> (ng/mL)	Geometric mean	707.0	1426.3	414.3	924.7	520.9	1113.4
	CV (%)	37.5	33.9	69.4	51.6	63.9	49.8
t <sub>max</sub> (hr)	Median	1.08	1.50	1.57	1.50	1.50	1.50
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Maximum	2.00	2.00	3.00	2.00	3.00	2.00
C <sub>ss,min</sub> (ng/mL)	Geometric mean	33.1	66.7	27.2	54.9	29.6	59.7
	CV (%)	113.5	74.4	99.9	66.9	102.9	69.0
CL/F (L/hr)	Mean	87.1	80.7	140.1	115.8	117.4	100.8
	SD	39.0	24.8	75.6	55.4	66.9	47.4
t <sub>1/2</sub> (hr)	Mean	3.17	5.52	2.77 <sup>b</sup>	5.52 <sup>b</sup>	2.96 <sup>c</sup>	5.52 <sup>c</sup>
	SD	0.99	1.38	0.56	0.77	0.80	1.07
Ael <sub>(u)</sub> (μg)	Mean	143.7	281.9	101.8	253.0	119.8	265.4
	SD	145.3	217.2	50.5	99.4	101.5	156.6
Fu (%)	Mean	0.072	0.070	0.051	0.063	0.060	0.066
	SD	0.073	0.054	0.025	0.025	0.051	0.039
CL <sub>R</sub> (L/hr)	Mean	0.063	0.053	0.070	0.077	0.067	0.067
	SD	0.083	0.036	0.052	0.058	0.065	0.050

<sup>a</sup> Number of subjects who received 400-mg morning dose on Day 13.

<sup>b</sup> Excludes 2 of 12 subjects for whom t<sub>1/2</sub> could not be calculated.

<sup>c</sup> Excludes 2 of 21 subjects for whom t<sub>1/2</sub> could not be calculated.

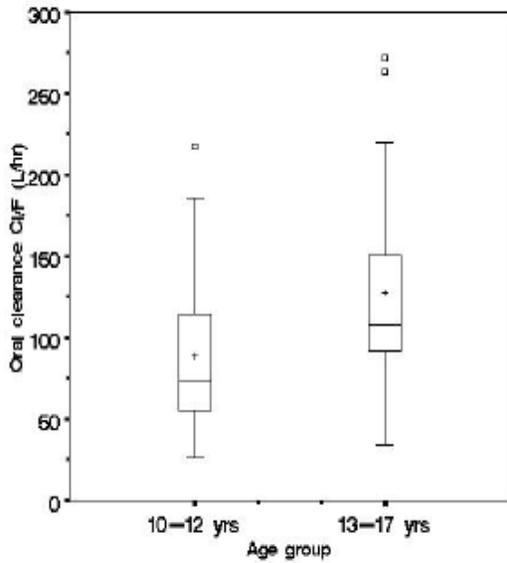
Ael<sub>(u)</sub> amount of metabolite eliminated. AUC<sub>ss</sub> area under the curve at steady-state. CL/F apparent oral clearance. CV coefficient of variation. CL<sub>R</sub> renal clearance from plasma. C<sub>ss,max</sub> maximum plasma concentration at steady-state. C<sub>ss,min</sub> minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t<sub>max</sub> time of maximum plasma concentration. t<sub>1/2</sub> terminal elimination half-life.

Exposure to quetiapine in terms of AUCss and C<sub>ss,max</sub> appeared to be higher in the 10- to 12-year-old subjects than in the 13- to 17-year-old subjects on Days 7 and 13. The geometric means for AUCss on Days 7 and 13 were 55% and 36% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 – 17 year old. The geometric means for C<sub>ss,max</sub> on Days 7 and 13 were 71% and 54% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 -17 year olds. The quetiapine C<sub>ss,min</sub> was 22% and 21% higher for the 10- to 12-year-old subjects on Days 7 and 13, respectively as compared to the 13 to 17 year olds. The apparent oral clearance (CL/F) was 38% and 30% lower for the 10- to 12-year-old subjects on Days 7 and 13, respectively as compared to 13 to 17 year olds.

Box plots of CL/F for all PK population subjects in each age group on Days 7 and 13 are presented in the following figure. A scatter plot of CL/F by age for Days 7 and 13 for all PK population subjects is presented in the following figure. The median CL/F was lower among 10- to 12-year-old subjects relative to the 13 to 17 year olds. Regression lines showed CL/F tended to

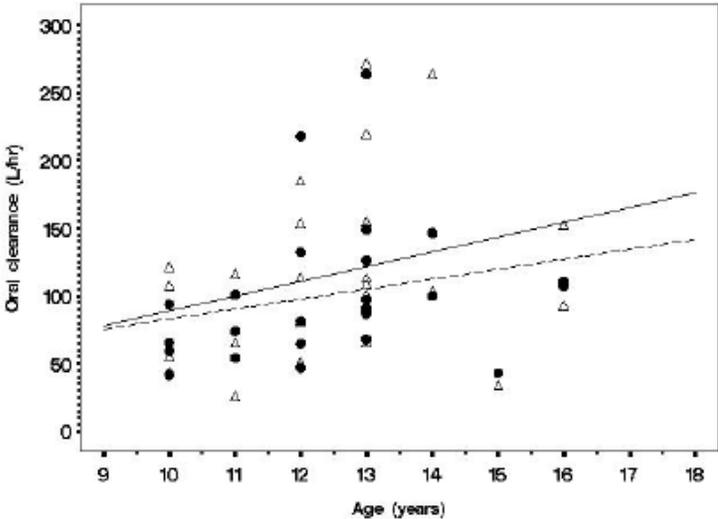
increase with age. However, there was large amount of overlap in the distributions of CL/F at all ages. Dose normalized AUC or Cmax does not appear to indicate a change in exposure when compared to the weight of the patient.

Box plots of oral clearance of quetiapine on Day 7 and Day 13 by age group



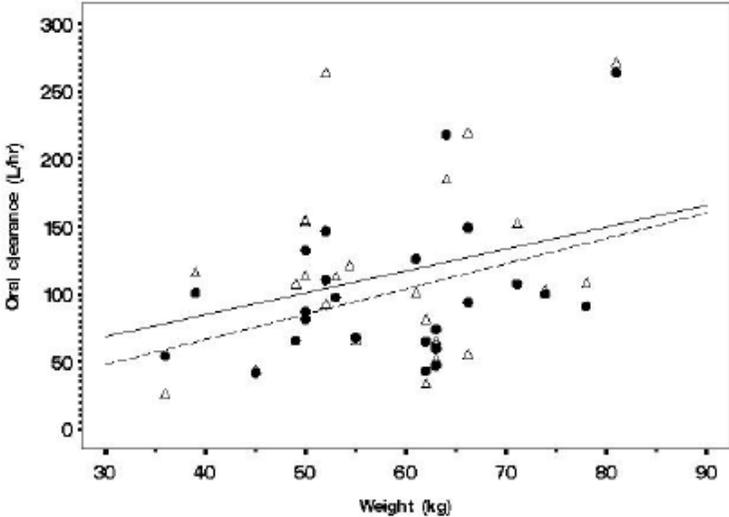
Note: The horizontal lines in the graph indicate the 10th,25th,50th,75th,and 90th percentiles

Scatter plot of oral clearance of quetiapine by age for Day 7 and Day 13



Triangle: Observed values for Day 7  
Dot: Observed values for Day 13  
Solid line: Linear regression for Day 7  
Dash line: Linear regression for Day 13

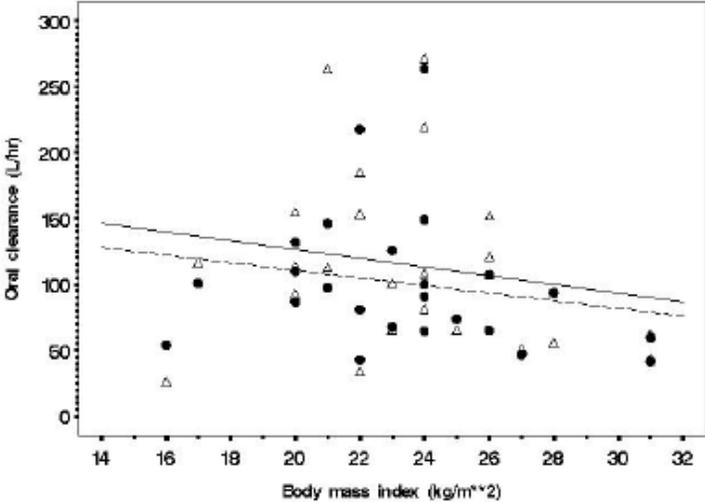
Scatter plot of oral clearance of quetiapine by weight for Day 7 and Day 13



Triangle: Observed values for Day 7  
Dot: Observed values for Day 13  
Solid line: Linear regression for Day 7  
Dash line: Linear regression for Day 13

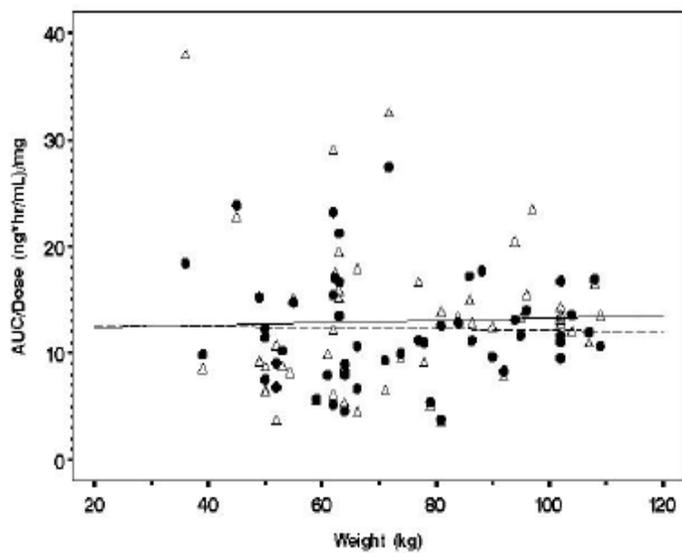
The clearance of quetiapine increase with age and weight of the patients. There was large inter-patient variability in the data.

Oral Clearance (CL/F) of quetiapine versus body mass index



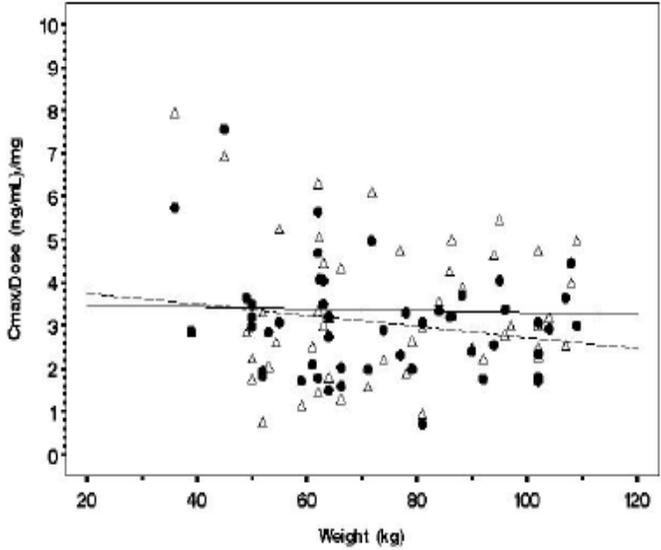
Triangle: Observed values for Day 7  
Dot: Observed values for Day 13  
Solid line: Linear regression for Day 7  
Dash line: Linear regression for Day 13

Dose-normalized AUC of quetiapine versus weight on combined data from children/adolescents and adults (data from study 41441C00130)



Triangle: Observed values on combined data from Day 7 (Children/Adolescents) and Day 6 (Adults)  
Dot: Observed values on combined data from Day 13 (Children/Adolescents) and Day 12 (Adults)  
Solid line: Linear regression on combined data from Day 7 (Children/Adolescents) and Day 6 (Adults)  
Dash line: Linear regression on combined data from Day 13 (Children/Adolescents) and Day 12 (Adults)

Dose-normalized C<sub>max</sub> of quetiapine versus weight on combined data from children/adolescents and adults

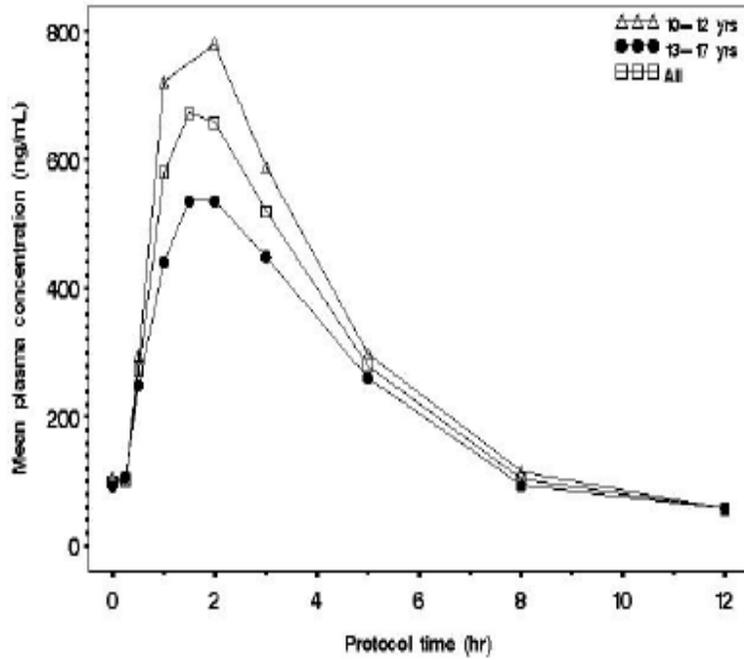


Triangle: Observed values on combined data from Day 7 (Children/Adolescents) and Day 6 (Adults)  
Dot: Observed values on combined data from Day 13 (Children/Adolescents) and Day 12 (Adults)  
Solid line: Linear regression on combined data from Day 7 (Children/Adolescents) and Day 6 (Adults)  
Dash line: Linear regression on combined data from Day 13 (Children/Adolescents) and Day 12 (Adults)

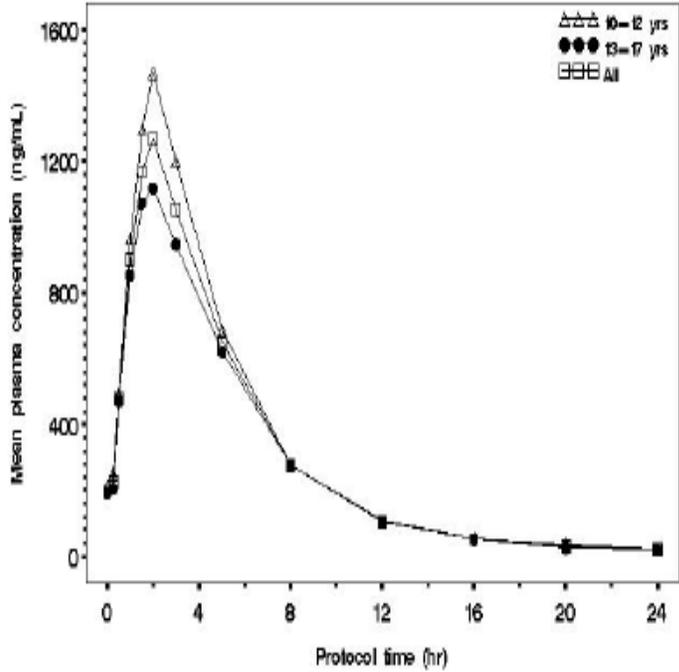
Metabolite pharmacokinetics

The following figures contain the plasma concentration time profile for the metabolites.

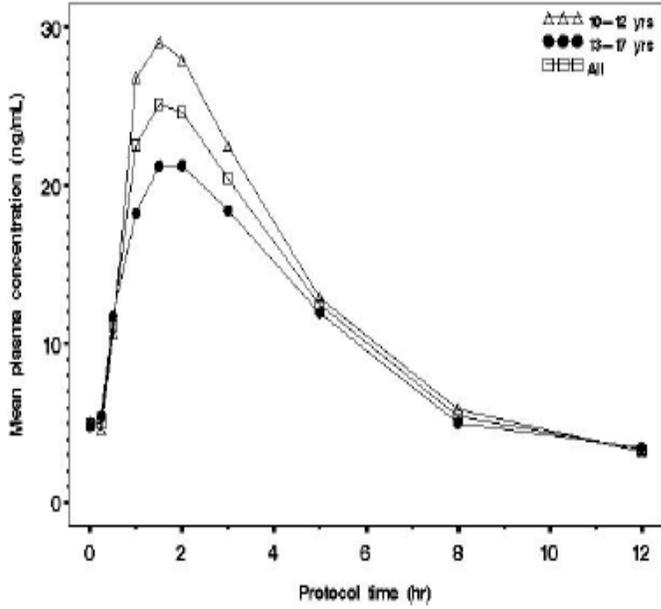
Mean plasma concentrations of quetiapine sulfoxide (IC1213841) over time on Day 7 for PK population subjects who received the 200 mg morning dose



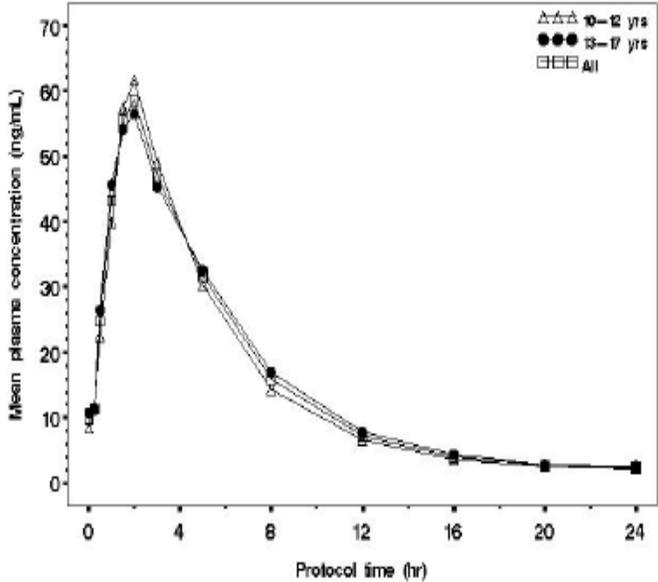
Mean plasma concentrations of quetiapine sulfoxide (ICI213,841) over time on Day 13 for PK population subjects who received the 400 mg morning dose



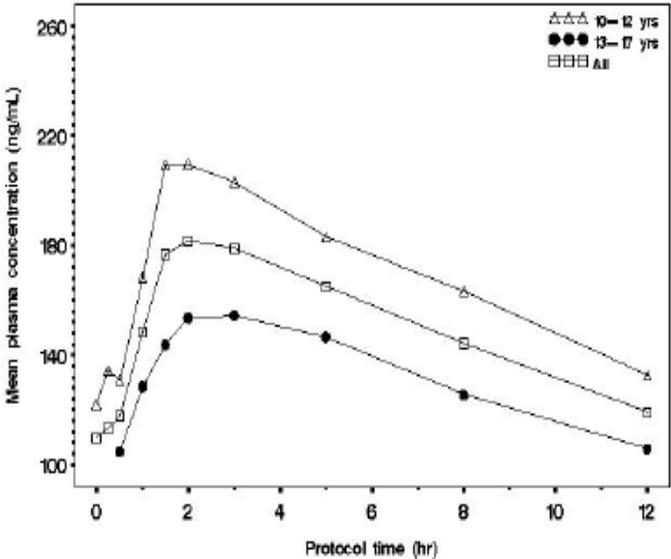
Mean plasma concentrations of 7-hydroxy quetiapine (ICI214,227) over time on Day 7 for PK population subjects who received the 200 mg morning dose



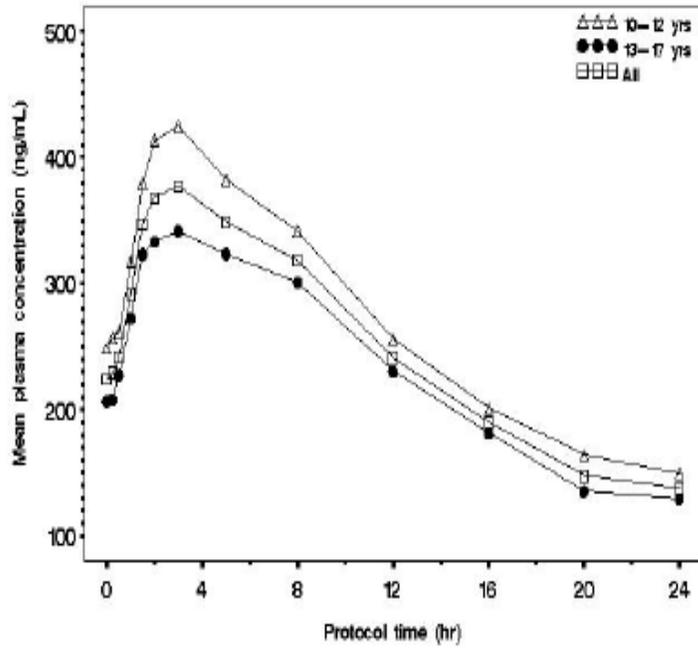
Mean plasma concentrations of 7-hydroxy quetiapine (ICI214,227) over time on Day 13 for PK population subjects who received the 400 mg morning dose



Mean plasma concentrations of N-desalkyl quetiapine (M211,803) over time on Day 7 for PK population subjects who received the 200 mg morning dose



Mean plasma concentrations of N-desalkyl quetiapine (M211,803) over time on Day 13 for PK population subjects who received the 400 mg morning dose



Pharmacokinetic parameters at steady-state are summarized for the 3 metabolites, quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine in the following tables.

Pharmacokinetic parameters for quetiapine sulfoxide for subjects who received 200 and 400-mg morning dose on Day 13

PK parameter	Statistic	Age group					
		10-12 yrs (n=9) <sup>a</sup>		13-17 yrs (n=12)		Total (n=21) <sup>a</sup>	
		Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC <sub>0-∞</sub> (ng*hr/mL)	Geometric mean	3374.8	6967.0	2585.8	5946.9	2898.4	6364.4
	CV (%)	21.5	26.5	40.3	33.0	35.5	30.8
C <sub>ss,max</sub> (ng/mL)	Geometric mean	795.9	1560.7	560.9	1170.5	651.7	1324.1
	CV (%)	25.5	24.1	34.4	37.6	35.4	35.2
t <sub>max</sub> (hr)	Median	1.67	1.50	1.57	1.75	1.63	1.50
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Maximum	2.02	3.00	3.00	5.00	3.00	5.00
C <sub>ss,min</sub> (ng/mL)	Geometric mean	45.2	92.3	44.5	96.4	44.8	94.7
	CV (%)	45.8	71.0	79.2	48.9	64.1	57.1
t <sub>1/2</sub> (hr)	Mean	2.79 <sup>b</sup>	5.64 <sup>b</sup>	2.53 <sup>c</sup>	4.98 <sup>c</sup>	2.64 <sup>d</sup>	5.27 <sup>d</sup>
	SD	0.45	0.98	0.50	1.17	0.49	1.11
Ael <sub>(ex)</sub> (μg)	Mean	1073.5	3253.8	1168.9	3910.2	1128.0	3628.9
	SD	806.4	2801.4	523.0	2193.9	642.6	2428.4
Fu (%)	Mean	0.515	0.781	0.561	0.938	0.541	0.871
	SD	0.387	0.672	0.251	0.527	0.308	0.583
CL <sub>cr</sub> (L/hr)	Mean	0.301	0.409	0.467	0.649	0.395	0.546
	SD	0.219	0.193	0.246	0.307	0.244	0.285

<sup>a</sup> Number of subjects who received 400-mg morning dose on Day 13.

<sup>b</sup> Excludes 1 of 9 subjects for whom t<sub>1/2</sub> could not be calculated.

<sup>c</sup> Excludes 2 of 12 subjects for whom t<sub>1/2</sub> could not be calculated.

<sup>d</sup> Excludes 3 of 21 subjects for whom t<sub>1/2</sub> could not be calculated.

Ael<sub>(ex)</sub> amount of metabolite eliminated. AUC<sub>0-∞</sub> area under the curve at steady-state. CL<sub>cr</sub> renal clearance from plasma.

C<sub>ss,max</sub> maximum plasma concentration at steady-state. C<sub>ss,min</sub> minimum plasma concentration at steady-state.

Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t<sub>max</sub> time of maximum plasma concentration. t<sub>1/2</sub> terminal elimination half-life.

Exposure to quetiapine sulfoxide in terms of AUCss and C<sub>ss,max</sub> were 30% and 40%, respectively higher on day 7 and 17% and 33% , respectively higher on day 13 in 10- to 12-year-old subjects than in 13- to 17-year-old subjects.

Pharmacokinetic parameters for 7-hydroxy quetiapine for subjects who received the 200 mg and 400 mg dose on day 13.

PK parameter	Statistic	Age group					
		10-12 yrs (n=9) <sup>a</sup>		13-17 yrs (n=12)		Total (n=21) <sup>a</sup>	
		Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC <sub>0-∞</sub> (ng*hr/mL)	Geometric mean	128.7	298.0	109.6	290.8	117.4	293.8
	CV (%)	31.3	40.8	50.3	54.8	42.8	47.9
C <sub>min,max</sub> (ng/mL)	Geometric mean	28.2	62.6	21.3	57.7	24.0	59.7
	CV (%)	39.2	37.4	46.5	57.5	45.1	48.5
t <sub>max</sub> (hr)	Median	2.00	2.00	1.57	1.50	1.82	1.50
	Minimum	1.00	1.00	0.52	0.50	0.52	0.50
	Maximum	3.00	3.00	3.00	2.00	3.00	3.00
C <sub>min</sub> (ng/mL)	Geometric mean	2.32	5.75	2.62	6.41	2.49	6.12
	CV (%)	53.2	58.0	87.7	71.9	72.0	64.5
t <sub>1/2</sub> (hr)	Mean	2.92 <sup>b</sup>	5.87 <sup>b</sup>	3.43 <sup>c</sup>	5.89 <sup>c</sup>	3.19 <sup>d</sup>	5.88 <sup>d</sup>
	SD	0.44	1.33	0.61	1.36	0.58	1.29
Ael <sub>(ex)</sub> (μg)	Mean	111.5	348.0	138.5	526.6	126.9	450.1
	SD	62.7	282.3	73.6	405.7	68.9	361.4
Fu (%)	Mean	0.054	0.084	0.066	0.126	0.061	0.108
	SD	0.030	0.068	0.035	0.097	0.033	0.087
CL <sub>R</sub> (L/hr)	Mean	0.853	1.049	1.204	1.531	1.053	1.324
	SD	0.500	0.426	0.620	0.738	0.586	0.658

<sup>a</sup> Number of subjects who received 400-mg morning dose on Day 13.

<sup>b</sup> Excludes 3 of 9 subjects for whom t<sub>1/2</sub> could not be calculated.

<sup>c</sup> Excludes 5 of 12 subjects for whom t<sub>1/2</sub> could not be calculated.

<sup>d</sup> Excludes 8 of 21 subjects for whom t<sub>1/2</sub> could not be calculated.

Ael<sub>(ex)</sub> amount of metabolite eliminated. AUC<sub>0-∞</sub> area under the curve at steady-state. CL<sub>R</sub> renal clearance from plasma.

C<sub>min,max</sub> maximum plasma concentration at steady-state. C<sub>min</sub> minimum plasma concentration at steady-state.

Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t<sub>max</sub> time of maximum plasma concentration. t<sub>1/2</sub> terminal elimination half-life.

There was about 17% and 3% higher AUCs for 7-hydroxy quetiapine in 10- to 12-year-old compared to 13 to 17 year old subjects on day 7 and 13, respectively. The C<sub>ss,max</sub> was 32% higher in 10- to 12-year-old compared to 13 to 17 year olds on Day 7 and about 9% on Day 13.

Pharmacokinetic parameters for N-desalkyl quetiapine for subjects who received the 200 mg and 400 mg morning dose

PK parameter <sup>b</sup>	Statistic	Age group					
		10-12 yrs (n=9) <sup>a</sup>		13-17 yrs (n=12)		Total (n=21) <sup>a</sup>	
		Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC <sub>ss</sub> (ng*hr/mL)	Geometric mean	1977.4	4074.0	1497.1	3380.7	1686.7	3662.1
	CV (%)	13.7	20.6	34.1	33.3	30.3	29.5
C <sub>ss,max</sub> (ng/mL)	Geometric mean	214.9	460.3	164.7	347.7	184.6	392.1
	CV (%)	18.8	23.4	33.8	36.5	31.0	34.2
t <sub>max</sub> (hr)	Median	2.00	2.00	3.00	3.00	3.00	3.00
	Minimum	1.00	1.50	1.00	1.50	1.00	1.50
	Maximum	12.00	8.00	8.00	8.00	12.00	8.00
C <sub>ss,min</sub> (ng/mL)	Geometric mean	126.9	250.4	100.2	223.5	110.8	234.7
	CV (%)	20.0	22.1	34.3	25.3	30.9	24.1
Ael <sub>(ex)</sub> (μg)	Mean	2231.1	5069.6	2328.3	5806.0	2286.7	5490.4
	SD	1813.9	3131.1	1776.0	4021.5	1747.4	3599.4
Fu (%)	Mean	1.448	1.645	1.511	1.884	1.484	1.782
	SD	1.178	1.016	1.153	1.305	1.134	1.168
CL <sub>R</sub> (L/hr)	Mean	1.052	1.210	1.610	1.755	1.371	1.521
	SD	0.776	0.704	1.514	1.466	1.258	1.207

<sup>a</sup> Number of subjects who received 400-mg morning dose on Day 13.

<sup>b</sup> t<sub>1/2</sub> results are omitted from this table as there were only 5 subjects who provided data on both Days 7 and 13.

Ael<sub>(ex)</sub> amount of metabolite eliminated. AUC<sub>ss</sub> area under the curve at steady-state. CL<sub>R</sub> renal clearance from plasma.

C<sub>ss,max</sub> maximum plasma concentration at steady-state. C<sub>ss,min</sub> minimum plasma concentration at steady-state.

Fu mole fraction (percent) of dose excreted in the urine. NA not applicable. SD standard deviation.

t<sub>max</sub> time of maximum plasma concentration. t<sub>1/2</sub> terminal elimination half-life.

The means for AUC<sub>ss</sub> for N-desalkyl quetiapine on Days 7 and 13 were 32% and 21% higher, respectively, for the 10- to 12-year-old subjects compared to 13 to 17 year olds. The means for C<sub>ss,max</sub> on Days 7 and 13 were 30% and 32% higher, respectively, for 10- to 12-year-old subjects compared to the 13 to 17 year old.

#### Summary of Pharmacokinetics

Two of the metabolites, quetiapine sulfoxide (t<sub>1/2</sub> = 5.27 hrs) and 7-hydroxy quetiapine (t<sub>1/2</sub> = 5.88 hrs), had estimates of t<sub>1/2</sub> similar to quetiapine (5.52 hrs). The N-desalkyl quetiapine metabolite (t<sub>1/2</sub> = 11.32 hrs) had a longer t<sub>1/2</sub> than quetiapine (t<sub>1/2</sub> = 5.52).

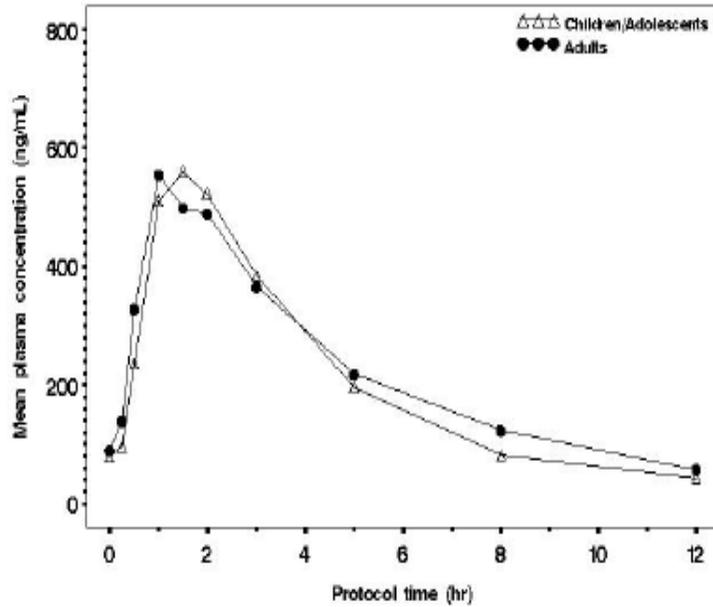
In terms of in vivo exposure, the rank order of exposure with respect to both AUC<sub>ss</sub> and C<sub>ss,max</sub> was: quetiapine sulfoxide > quetiapine > N-desalkyl quetiapine > 7-hydroxy quetiapine.

Quetiapine AUC<sub>ss</sub> and C<sub>ss,max</sub> appeared to be higher in 10- to 12-year-old subjects than in 13- to 17-year-old subjects. Similar trends were observed for the quetiapine sulfoxide and N-desalkyl quetiapine metabolites. There was high degree of inter-subject variability in exposure to quetiapine and its metabolites in both subject populations. There was no apparent association between AUC and C<sub>max</sub> with weight for quetiapine.

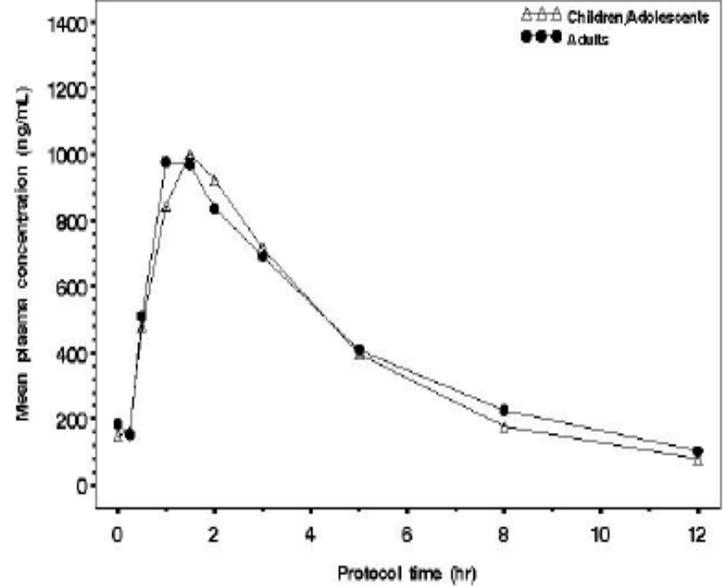
Comparison of pharmacokinetic results with those from Study D144C100130

The following figures contain the mean plasma concentrations over time for quetiapine in subjects who received 200 mg morning dose on combined data from children/adolescents and adults from study D1441C00130

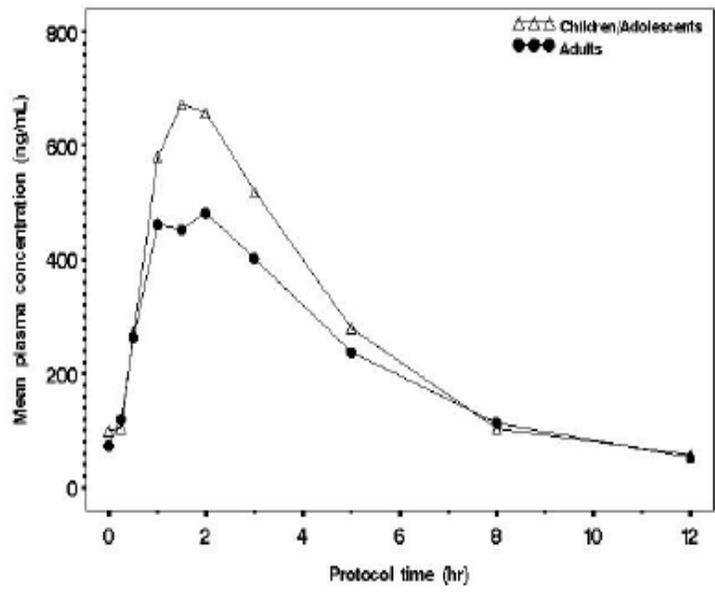
Mean plasma concentrations for quetiapine over time for PK population subjects who received the 200 mg morning dose on combined data from children/adolescents and adults



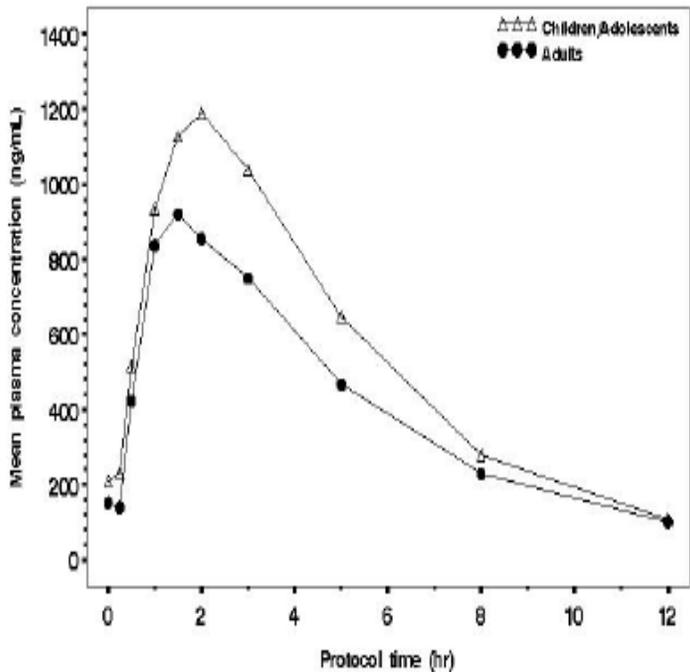
Mean plasma concentrations of quetiapine over time for PK population subjects who received the 400 mg morning dose on combined data from children/adolescents and adults



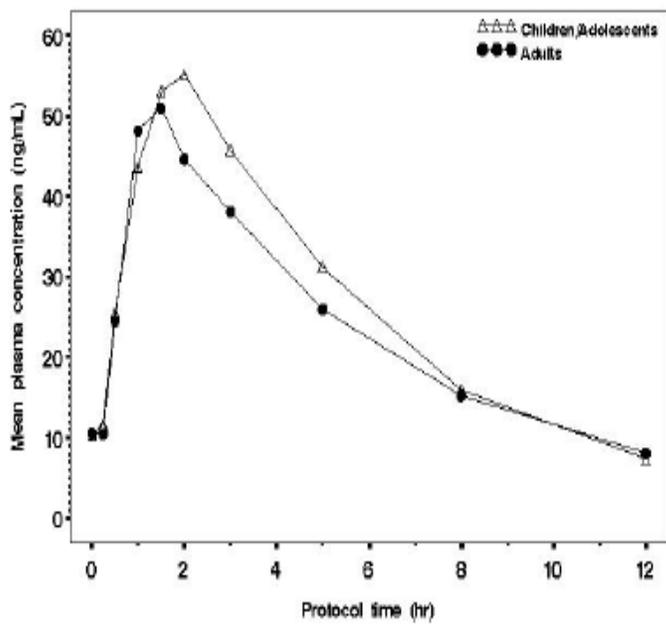
Mean plasma concentrations of quetiapine sulfoxide over time for subjects who received 200 mg morning dose on combined data from children/adolescents and adults



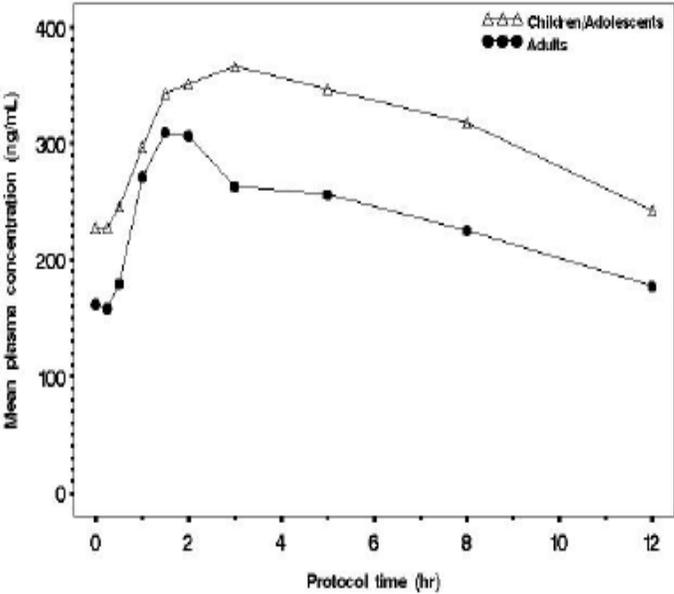
Mean plasma concentrations of quetiapine sulfoxide over time for subjects who received 400 mg morning dose on combined data from children/adolescents and adults



Mean plasma concentrations of 7-hydroxy quetiapine (ICI214,227) over time for PK population subjects who received the 400 mg morning dose on combined data from children/adolescents and adults (data from study D1441C00130)



Mean plasma concentrations of N-desalkyl quetiapine (M211,803) over time for PK population subjects who received the 400 mg morning dose on combined data from children/adolescents and adults (data from study D1441C00130)



The results of the comparisons of dose-normalized AUC<sub>ss</sub> and C<sub>ss,max</sub> for quetiapine and the 3 metabolites between children/adolescents and adults are presented in the following table.

Comparison of dose-normalized exposure (AUC<sub>ss</sub> and C<sub>max</sub>) to quetiapine and 3 metabolites in children/adolescents with exposure in adults in Study D1441C00130

Analyte	Dose-normalized AUC <sub>ss</sub>		Dose-normalized C <sub>ss,max</sub>	
	Mean ratio <sup>a</sup>	90% CI	Mean ratio <sup>a</sup>	90% CI
Quetiapine	0.88	0.76, 1.03	0.92	0.79, 1.06
Quetiapine sulfoxide	1.27	1.15, 1.39	1.30	1.16, 1.44
7-hydroxy quetiapine	1.08	0.92, 1.26	1.11	0.94, 1.31
N-desalkyl quetiapine	1.45	1.30, 1.61	1.31	1.15, 1.49

<sup>a</sup> Ratio (10- to 17-year-olds:adults) of least squares means from ANOVA model.  
ANOVA analysis of variance. AUC<sub>ss</sub> area under the curve at steady-state. CI confidence interval. C<sub>ss,max</sub> maximum plasma concentration at steady-state.

The comparisons of dose-normalized exposure in children/adolescents with that in adults showed no evidence for age-related differences in exposure to quetiapine or its CYP2D6 metabolite, 7-hydroxy quetiapine. The effect of age on exposure to quetiapine sulfoxide, as measured by AUC<sub>ss</sub>, showed statistical significance, with about 27% higher exposure seen in younger subjects. The effect of age on exposure to quetiapine sulfoxide, as measured by C<sub>ss,max</sub>, was statistically significant, with about 30% higher peak exposure seen in younger subjects.

When AUC<sub>ss</sub> and C<sub>ss,max</sub> were normalized by the weight-adjusted dose (i.e. were divided by [dose/weight]), no differences in exposure with age were apparent for quetiapine sulfoxide or N-desalkyl quetiapine. For quetiapine and 7-hydroxy significant differences were observed.

Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites on combined data from children/adolescents and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Children and Adolescents/Adults)			Children/Adolescents			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.59	0.50	0.70	610.69	527.56	706.92	1035.06	900.34	1189.93
AUC (Quetiapine sulfoxide)	0.85	0.77	0.93	905.16	832.58	984.08	1070.64	989.32	1159.65
AUC (7-hydroxy quetiapine)	0.72	0.61	0.84	39.19	34.34	44.73	54.50	47.40	62.66
AUC (N-desalkyl quetiapine)	0.96	0.86	1.07	515.11	472.96	561.01	537.17	483.67	596.59
Cmax (Quetiapine)	0.61	0.53	0.71	160.07	139.17	184.10	261.76	232.12	295.19
Cmax (Quetiapine sulfoxide)	0.86	0.79	0.95	198.50	183.40	214.85	229.59	211.40	249.34
Cmax (7-hydroxy quetiapine)	0.74	0.63	0.87	7.99	7.04	9.07	10.83	9.31	12.59
Cmax (N-desalkyl quetiapine)	0.87	0.76	1.00	55.64	50.60	61.19	63.79	56.24	72.36

Comparisons of weight-adjusted, dose normalized exposure showed evidence for statistically significant age-related differences in exposure to quetiapine and 7-hydroxy quetiapine, with (41% lower AUC, 39 % lower Cmax for quetiapine; 28% lower AUC, 26% lower Cmax for 7-hydroxyquetiapine) lower exposures seen in younger children/adolescents. These comparisons of weight-adjusted, dose-normalized exposure showed no evidence for age-related differences in exposure to the quetiapine sulfoxide or N-desalkyl quetiapine metabolites.

#### Conclusions:

The sponsor concluded that comparisons of dose-normalized exposure in children/adolescents with that in adults showed no evidence for age-related differences in exposure to quetiapine or its CYP2D6 metabolite, 7-hydroxy quetiapine. However, these analyses showed statistically significant differences in the quetiapine sulfoxide and N-desalkyl quetiapine metabolites, with higher exposures seen in children/adolescents.

Comparisons of weight-adjusted, dose normalized exposure showed evidence for statistically significant age-related differences in exposure to quetiapine and 7-hydroxy quetiapine, with lower exposures seen in younger children/adolescents ((41% lower AUC, 39 % lower Cmax for quetiapine; 28% lower AUC, 26% lower Cmax for 7-hydroxyquetiapine). The comparisons of weight-adjusted, dose-normalized exposure showed no evidence for age-related differences in exposure to the quetiapine sulfoxide (27% increase in AUC) or N-desalkyl quetiapine (45% increase in AUC) metabolites. There was large variability in the data.

Safety summary: The sponsor reported that quetiapine was well tolerated in this population of children and adolescents ages 10 to 17 years with diagnoses of bipolar I disorder or schizoaffective disorder. There were no deaths or other serious AEs during study treatment. There were no unexpected AEs reported during the study. The sponsor reported that there were no obvious differences between the age groups in the types of adverse events that occurred, or in their intensity. Three subjects in the 10- to 12-year-old age group had their study medication doses restricted to 600 mg/day from Day 11 onward. Somnolence was the most frequently occurring AE during study treatment. Most of the cases of somnolence occurred shortly after initiation of study treatment (ie, Day 1 or 2) and resolved prior to study completion; all cases were rated by the investigators as mild in intensity and were considered treatment related.

*Reviewer comments: There was a trend towards higher exposures (36% to 55% higher AUC) in the younger children (10- 12 years old) when compared to adolescents (13 -17 year olds). There was large inter patient variability in the data.*

*Comparisons across studies indicated that dose normalized exposures in children/adolescents (10-17 years) were 12% lower AUC than adults. When adjusted for weight and dose, there appears to be significant differences in exposure to quetiapine and its 7-hydroxy metabolite with children/adolescents having lower (about 30-40% lower) than adults.*

Figure 11.2.1.1.2 Individual values of C<sub>max</sub> of quetiapine versus quetiapine dose

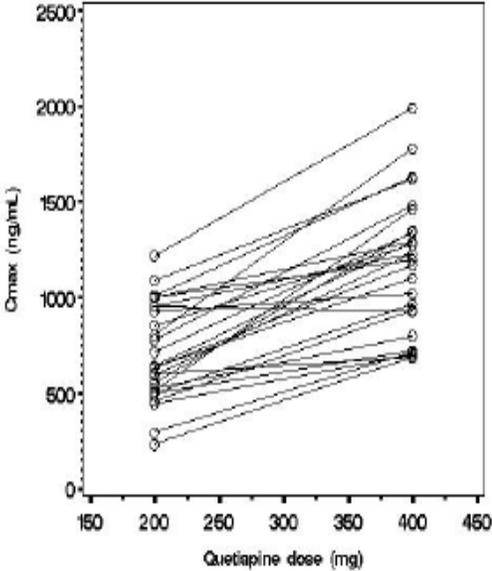


Figure 11.2.1.1.1.1 Individual values of AUC of quetiapine versus quetiapine dose

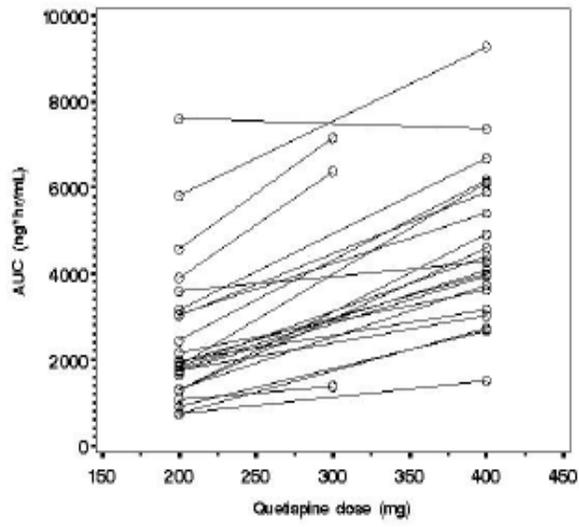


Figure 11.2.1.3.1.3 Box-plot of oral clearance (CL/F) of quetiapine on Day 7 and Day 13 by age group

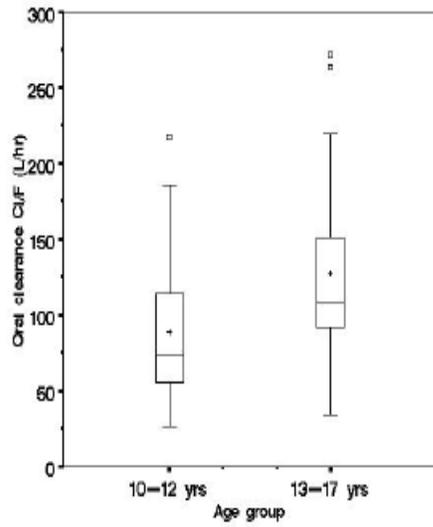


Table 11.2.1.1.1 Summary statistics for quetiapine pharmacokinetic parameter estimates  
 PK evaluable subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group					
		10-12 (N=9)		13-17 (N=12)		All (N=21)	
		Day 7	Day 13	Day 7	Day 13	Day 7	Day 13
AUC (ng*hr/mL)	N	9	9	12	12	21	21
	Mean	2944.446	5324.121	1962.911	4143.432	2383.569	4649.442
	SD	1911.482	1406.690	1383.731	1956.123	1662.026	1804.024
	Minimum	1302.25	3024.48	735.90	1517.21	735.90	1517.21
	Median	2443.15	5404.50	1806.18	3860.78	1860.32	4267.48
	Maximum	7603.48	7371.14	5821.13	9273.16	7603.48	9273.16
	Geometric Mean	2560.018	5144.961	1651.433	3784.823	1992.752	4317.077
	CV(%)	56.825	29.120	64.538	46.617	65.048	42.348
	Cmax (ng/mL)	N	9	9	12	12	21
Mean		755.667	1496.667	498.583	1016.083	608.762	1222.048
SD		338.116	498.122	338.859	422.324	354.793	506.771
Minimum		449.00	810.00	150.00	288.00	150.00	288.00
Median		658.00	1400.00	396.00	989.00	570.00	1190.00
Maximum		1590.00	2300.00	1260.00	1880.00	1590.00	2300.00
Geometric Mean		707.001	1426.254	414.267	924.704	520.017	1113.416
CV(%)		37.455	33.860	69.351	51.606	63.852	49.802
tmax (hr)		N	9	9	12	12	21
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Median	1.08	1.50	1.57	1.50	1.50	1.50

Table 11.2.1.1.1 Summary statistics for quetiapine pharmacokinetic parameter estimates  
 - PK evaluable subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group					
		10-12 (N=9)		13-17 (N=12)		All (N=21)	
		Day 7	Day 13	Day 7	Day 13	Day 7	Day 13
$t_{max}$ (hr)	Maximum	2.00	2.00	3.00	2.00	3.00	2.00
C <sub>min</sub> (ng/mL)	N	9	9	12	12	21	21
	Mean	44.998	79.922	37.618	66.167	40.781	72.062
	SD	31.026	48.526	35.297	48.259	32.928	47.655
	Minimum	8.68	21.40	7.07	21.39	7.07	21.39
	Median	51.90	57.50	28.10	48.55	29.60	53.79
	Maximum	86.20	168.00	131.00	192.00	131.00	192.00
	Geometric Mean	33.141	66.680	27.186	54.911	29.595	59.677
	CV (%)	113.547	74.366	99.946	66.851	102.917	68.953
	CL/F (L/hr)	N	9	9	12	12	21
Mean		87.088	80.743	140.070	115.785	117.363	109.767
SD		38.995	24.764	75.579	55.366	66.872	47.403
Minimum		26.30	54.27	34.36	43.14	26.30	43.14
Median		81.86	74.01	110.78	103.73	107.51	93.73
Maximum		153.58	132.25	271.78	263.64	271.78	263.64
Geometric Mean		78.124	77.746	121.107	105.685	100.364	92.655
CV (%)		56.825	29.120	64.538	46.617	65.048	42.348
$t_{1/2}$ (hr)		N	9	9	10	10	19
	Mean	3.173	5.519	2.770	5.520	2.961	5.519

Table 11.2.1.2.1 Summary statistics for quetiapina sulfoxide (ICI213,841) pharmacokinetic parameter estimates  
 - PK evaluable subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter	Age Group						
	N	10-12 (N=9)		13-17 (N=12)		All (N=21)	
		Day 7	Day 13	Day 7	Day 13	Day 7	Day 13
AUC (ng*hr/mL)	N	9	9	12	12	21	21
	Mean	3447.097	7214.171	2774.863	6204.493	3062.963	6637.212
	SD	797.009	2339.193	1134.961	1725.542	1038.637	2022.003
	Minimum	2610.65	5614.28	1302.39	2669.27	1302.39	2669.27
	Median	3292.88	6383.88	2425.70	5919.73	2847.62	6120.56
	Maximum	5170.39	13188.45	5175.32	8972.51	5175.32	13188.45
	Geometric Mean	3374.796	6966.982	2588.777	5946.904	2898.398	6364.391
	CV(%)	21.511	26.514	40.262	33.025	35.542	30.787
	Cmax (ng/mL)	N	9	9	12	12	21
Mean		618.556	1600.000	591.667	1232.917	688.905	1390.238
SD		206.484	374.066	212.464	375.599	234.775	410.136
Minimum		543.00	1090.00	316.00	435.00	316.00	435.00
Median		738.00	1650.00	549.50	1205.00	640.00	1300.00
Maximum		1130.00	2170.00	1020.00	2070.00	1130.00	2170.00
Geometric Mean		795.937	1560.748	560.943	1170.454	651.695	1324.087
CV(%)		25.482	24.129	34.432	37.634	35.432	35.196
tmax (hr)		N	9	9	12	12	21
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Median	1.67	1.50	1.57	1.75	1.63	1.50

Table 11.2.1.2.1 Summary statistics for quetiapine sulfoxide (ICI213,841) pharmacokinetic parameter estimates - PK evaluable subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group					
		10-12 (N=9)		13-17 (N=12)		All (N=21)	
		Day 7	Day 13	Day 7	Day 13	Day 7	Day 13
tmax (hr)	Maximum	2.02	3.00	3.00	5.00	3.00	5.00
	N	9	9	12	12	21	21
Cmin (ng/mL)	Mean	48.622	108.356	56.900	106.767	53.352	107.448
	SD	17.103	62.397	47.903	52.488	37.373	55.437
	Minimum	19.30	26.80	17.70	45.80	17.70	26.80
	Median	55.50	108.00	34.50	88.00	51.20	102.00
	Maximum	69.30	249.00	185.00	204.00	185.00	249.00
	Geometric Mean	45.195	92.339	44.452	96.441	44.769	94.661
	CV(N)	45.801	71.011	79.188	48.917	64.074	57.054
	N	9	9	12	12	21	21
t1/2 (hr)	Mean	2.791	5.636	2.526	4.980	2.644	5.272
	SD	0.453	0.979	0.504	1.170	0.487	1.110
	Minimum	2.28	4.48	1.83	3.77	1.83	3.77
	Median	2.72	5.77	2.53	4.60	2.54	4.99
	Maximum	3.45	7.13	3.54	7.32	3.54	7.32
	N	8	8	10	10	18	18
	Mean	0.284	0.126	0.284	0.145	0.271	0.137
	SD	0.039	0.021	0.055	0.030	0.050	0.027
Lambda_z (hr <sup>-1</sup> )	Minimum	0.20	0.10	0.20	0.09	0.20	0.09
	N	8	8	10	10	18	18

Table 11.2.1.3.1 Summary statistics for 7-hydroxy quetiapine (ICI214,227) pharmacokinetic parameter estimates  
- PK available subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group					
		10-12 (N=9)		13-17 (N=12)		All (N=21)	
		Day 7	Day 13	Day 7	Day 13	Day 7	Day 13
AUC (ng*hr/mL)	N	9	9	12	12	21	21
	Mean	134.354	320.233	123.825	331.137	128.338	326.464
	SD	43.633	138.037	76.473	192.565	63.297	167.472
	Minimum	87.56	170.42	72.63	145.44	72.63	145.44
	Median	120.46	283.60	90.05	263.14	109.61	263.99
	Maximum	225.30	628.31	333.59	762.56	333.59	762.56
	Geometric Mean	128.691	297.995	109.590	290.751	117.402	293.834
	CV(%)	31.321	40.804	50.299	54.806	42.787	47.856
	Cmax (ng/mL)	N	9	9	12	12	21
Mean		29.933	66.233	23.625	66.092	26.329	66.152
SD		10.380	23.400	13.557	37.923	12.427	31.781
Minimum		15.70	34.90	13.50	28.90	13.50	28.90
Median		29.90	61.50	18.60	54.70	22.70	61.50
Maximum		43.80	99.20	61.30	139.00	61.30	139.00
Geometric Mean		28.199	62.563	21.260	57.694	23.996	59.732
CV(%)		39.178	37.404	46.464	57.452	48.099	48.461
tmax (hr)		N	9	9	12	12	21
	Minimum	1.00	1.00	0.52	0.50	0.52	0.50
	Median	2.00	2.00	1.57	1.50	1.82	1.50

Table 11.2.1.4.1 Summary statistics for N-desalkyl quetiapine (M211,803) pharmacokinetic parameter estimates - PK evaluable subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter	Age Group						
	N	10-12 (N=9)		13-17 (N=12)		All (N=21)	
		Day 7	Day 13	Day 7	Day 13	Day 7	Day 13
AUC (ng*hr/mL)	N	9	9	12	12	21	21
	Mean	1994.622	4151.463	1573.816	3543.345	1754.161	3803.967
	SD	290.800	874.543	519.091	1115.114	477.033	1041.603
	Minimum	1703.13	3027.50	850.90	2048.61	850.90	2048.61
	Median	1874.17	4020.25	1399.49	3272.07	1840.85	3716.88
	Maximum	2631.19	5845.24	2431.36	5638.58	2631.19	5845.24
	Geometric Mean	1977.446	4073.993	1497.113	3380.731	1686.737	3662.090
	CV(%)	13.718	20.605	34.072	33.284	30.289	29.485
	Cmax (ng/mL)	N	9	9	12	12	21
Mean		218.222	470.778	173.333	368.667	192.571	412.429
SD		40.567	101.335	60.527	136.030	56.492	130.253
Minimum		155.00	287.00	108.00	209.00	108.00	209.00
Median		212.00	474.00	152.50	336.00	201.00	430.00
Maximum		281.00	613.00	308.00	649.00	308.00	649.00
Geometric Mean		214.891	460.291	164.651	347.667	184.557	392.097
CV(%)		18.818	23.440	33.812	36.533	30.988	34.189
tmax (hr)		N	9	9	12	12	21
	Minimum	1.00	1.50	1.00	1.50	1.00	1.50
	Median	2.00	2.00	3.00	3.00	3.00	3.00
	Maximum						

Table 11.2.1.4.1 Summary statistics for N-desalkyl quetiapine (M11,803) pharmacokinetic parameter estimates - PK evaluable subjects who received 400 mg morning doses on Day 13

Pharmacokinetic Parameter		Age Group					
		10-12 (N=9)		13-17 (N=12)		All (N=21)	
		Day 7	Day 13	Day 7	Day 13	Day 7	Day 13
tmax (hr)	Maximum	12.00	8.00	8.00	8.00	12.00	8.00
	N	9	9	12	12	21	21
Cmin (ng/mL)	Mean	129.222	255.667	105.825	230.000	115.852	241.000
	SD	27.317	54.884	40.048	58.429	36.351	57.026
	Minimum	101.00	170.00	68.40	148.00	68.40	148.00
	Median	120.00	248.00	97.80	221.00	104.00	225.00
	Maximum	186.00	351.00	204.00	356.00	204.00	356.00
	Geometric Mean	126.895	250.400	100.150	223.523	110.842	234.669
	CV(%)	20.000	22.060	34.285	25.262	30.905	24.076
	N	2	2	3	3	5	5
t1/2 (hr)	Mean	9.260	14.695	8.153	8.750	8.596	11.128
	SD	1.131	6.682	0.815	1.217	1.010	4.744
	Minimum	8.46	9.97	7.61	7.35	7.61	7.35
	Median	9.26	14.70	7.76	9.34	8.46	9.56
	Maximum	10.06	19.42	9.09	9.56	10.06	19.42
	N	2	2	3	3	5	5
	Mean	0.075	0.055	0.087	0.077	0.082	0.068
SD	0.007	0.021	0.006	0.012	0.008	0.018	
Minimum	0.07	0.04	0.08	0.07	0.07	0.04	



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Table 11.2.1.1.2 Summary statistics for quetiapine pharmacokinetic parameter estimates - PK evaluable subjects who received 300 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group			
		16-12 (N=3)		All (N=3)	
		Day 7	Day 13	Day 7	Day 13
tmax (hr)	Maximum	1.33	3.00	1.33	3.00
	N	3	3	3	3
Cmin (ng/mL)	Mean	61.833	126.067	61.833	126.067
	SD	28.899	94.716	28.899	94.716
	Minimum	31.00	27.20	31.00	27.20
	Median	66.20	135.00	66.20	135.00
	Maximum	88.30	216.00	88.30	216.00
	Geometric Mean	56.588	92.566	56.588	92.566
	CV(%)	58.276	150.163	58.276	150.163
	N	3	3	3	3
	Mean	93.481	102.226	93.481	102.226
CL/F (L/hr)	SD	79.662	100.062	79.662	100.062
	Minimum	43.79	41.90	43.79	41.90
	Median	51.29	47.05	51.29	47.05
	Maximum	185.36	217.73	185.36	217.73
	Geometric Mean	74.668	75.432	74.668	75.432
	CV(%)	93.313	115.348	93.313	115.348
	N	2	2	2	2
	Mean	3.360	4.185	3.360	4.185

Table 11.2.1.1.2 Summary statistics for quetiapine pharmacokinetic parameter estimates  
 - PK evaluable subjects who received 300 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group			
		10-12 (N=3)		All (N=3)	
		Day 7	Day 13	Day 7	Day 13
Fu (%)	Mean	0.038	0.050	0.038	0.050
	SD	0.046	0.061	0.046	0.061
	Minimum	0.01	0.01	0.01	0.01
	Median	0.04	0.05	0.04	0.05
	Maximum	0.07	0.09	0.07	0.09
	CLr (L/hr)	N	2	2	2
Mean		0.023	0.029	0.023	0.029
SD		0.018	0.021	0.018	0.021
Minimum		0.01	0.01	0.01	0.01
Median		0.02	0.03	0.02	0.03
Maximum		0.04	0.04	0.04	0.04

Table 11.2.5.1 Comparison of dose-normalized AUC and C<sub>max</sub> of quetiapine and 3 metabolites on combined data from children/adolescents and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Children and Adolescents/Adults)			Children/Adolescents			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.88	0.76	1.03	10.64	9.13	12.41	12.05	10.77	13.48
AUC (Quetiapine sulfoxide)	1.27	1.15	1.39	15.78	14.37	17.32	12.46	11.62	13.38
AUC (7-hydroxy quetiapine)	1.08	0.92	1.26	0.68	0.60	0.78	0.63	0.55	0.73
AUC (N-desalkyl quetiapine)	1.45	1.30	1.61	8.98	8.23	9.79	6.21	5.65	6.82
C <sub>max</sub> (Quetiapine)	0.92	0.79	1.06	2.79	2.39	3.26	3.05	2.76	3.37
C <sub>max</sub> (Quetiapine sulfoxide)	1.30	1.16	1.44	3.46	3.14	3.82	2.67	2.45	2.91
C <sub>max</sub> (7-hydroxy quetiapine)	1.11	0.94	1.31	0.14	0.12	0.16	0.13	0.11	0.15
C <sub>max</sub> (N-desalkyl quetiapine)	1.31	1.15	1.49	0.97	0.86	1.07	0.74	0.66	0.84

Table 11.2.5.2 Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites on combined data from children/adolescents and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Children and Adolescents/Adults)			Children/Adolescents			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.59	0.50	0.70	610.69	527.56	706.92	1035.06	900.34	1189.93
AUC (Quetiapine sulfoxide)	0.85	0.77	0.93	905.16	832.58	984.08	1070.64	989.32	1158.65
AUC (7-hydroxy quetiapine)	0.72	0.61	0.84	39.19	34.34	44.73	54.50	47.40	62.66
AUC (N-desalkyl quetiapine)	0.96	0.86	1.07	515.11	472.96	561.01	537.17	483.67	596.59
Cmax (Quetiapine)	0.61	0.53	0.71	160.07	139.17	184.10	261.76	232.12	295.19
Cmax (Quetiapine sulfoxide)	0.86	0.79	0.95	198.50	183.40	214.85	229.59	211.40	249.34
Cmax (7-hydroxy quetiapine)	0.74	0.63	0.87	7.99	7.04	9.07	10.83	9.31	12.59
Cmax (N-desalkyl quetiapine)	0.87	0.76	1.00	55.64	50.60	61.19	63.79	56.24	72.36

Table 4.1 Comparison of dose-normalized AUC, C<sub>max</sub> and C<sub>min</sub> of quetiapine and 3 metabolites on combined data from children (10-12 years old) and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Children (10-12 years old)/Adults)			Children (10-12 years old)			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	1.06	0.88	1.26	12.72	10.34	15.65	12.05	10.77	13.48
AUC (Quetiapine sulfoxide)	1.43	1.29	1.58	17.86	16.19	19.70	12.48	11.61	13.41
AUC (7-hydroxy quetiapine)	1.16	0.97	1.40	0.74	0.63	0.86	0.63	0.55	0.73
AUC (N-desalkyl quetiapine)	1.63	1.44	1.84	10.08	9.17	11.08	6.20	5.63	6.82
C <sub>max</sub> (Quetiapine)	1.16	0.99	1.35	3.52	2.96	4.19	3.05	2.76	3.37
C <sub>max</sub> (Quetiapine sulfoxide)	1.53	1.37	1.72	4.15	3.78	4.55	2.70	2.48	2.94
C <sub>max</sub> (7-hydroxy quetiapine)	1.23	1.00	1.51	0.16	0.13	0.18	0.13	0.11	0.15
C <sub>max</sub> (N-desalkyl quetiapine)	1.49	1.26	1.75	1.11	0.98	1.25	0.74	0.66	0.84
C <sub>min</sub> (Quetiapine)	0.79	0.59	1.04	0.19	0.13	0.26	0.24	0.20	0.28
C <sub>min</sub> (Quetiapine sulfoxide)	1.12	0.91	1.37	0.26	0.20	0.32	0.23	0.20	0.26
C <sub>min</sub> (7-hydroxy quetiapine)	0.86	0.69	1.08	0.01	0.01	0.02	0.02	0.01	0.02
C <sub>min</sub> (N-desalkyl quetiapine)	1.59	1.41	1.78	0.65	0.59	0.72	0.41	0.38	0.45

Table 4.2 Comparison of dose-normalized AUC, C<sub>max</sub> and C<sub>min</sub> of quetiapine and 3 metabolites on combined data from adolescents (13-17 years old) and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Adolescents (13-17 years old)/Adults)			Adolescents (13-17 years old)			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.73	0.61	0.88	8.84	7.11	10.99	12.05	10.77	13.48
AUC (Quetiapine sulfoxide)	1.11	0.99	1.25	13.86	11.93	16.11	12.48	11.61	13.41
AUC (7-hydroxy quetiapine)	1.00	0.81	1.22	0.63	0.51	0.78	0.63	0.55	0.73
AUC (N-desalkyl quetiapine)	1.28	1.12	1.47	7.95	6.93	9.13	6.20	5.63	6.82
C <sub>max</sub> (Quetiapine)	0.72	0.60	0.86	2.19	1.73	2.76	3.05	2.76	3.37
C <sub>max</sub> (Quetiapine sulfoxide)	1.06	0.93	1.21	2.86	2.48	3.31	2.70	2.48	2.94
C <sub>max</sub> (7-hydroxy quetiapine)	0.98	0.78	1.22	0.12	0.10	0.15	0.13	0.11	0.15
C <sub>max</sub> (N-desalkyl quetiapine)	1.14	0.96	1.35	0.85	0.73	0.97	0.74	0.66	0.84
C <sub>min</sub> (Quetiapine)	0.58	0.44	0.76	0.14	0.10	0.18	0.24	0.20	0.28
C <sub>min</sub> (Quetiapine sulfoxide)	1.01	0.82	1.25	0.23	0.18	0.30	0.23	0.20	0.26
C <sub>min</sub> (7-hydroxy quetiapine)	0.84	0.66	1.08	0.01	0.01	0.02	0.02	0.01	0.02
C <sub>min</sub> (N-desalkyl quetiapine)	1.29	1.14	1.46	0.53	0.47	0.60	0.41	0.38	0.45

Table 4.3 Comparison of dose-normalized AUC, C<sub>max</sub>, and C<sub>min</sub> of quetiapine and 3 metabolites on combined data from children (10-12 years old) and adolescents (13-17 years old)

Pharmacokinetic Parameter	Comparison (Children/Adolescents)			Children (10-12 years old)			Adolescents (13-17 years old)		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	1.44	1.13	1.84	12.72	10.34	15.65	8.84	7.11	10.99
AUC (Quetiapine sulfoxide)	1.29	1.11	1.49	17.86	16.19	19.70	13.86	11.93	16.11
AUC (7-hydroxy quetiapine)	1.17	0.94	1.44	0.74	0.63	0.86	0.63	0.51	0.78
AUC (N-desalkyl quetiapine)	1.27	1.11	1.45	10.08	9.17	11.08	7.95	6.93	9.13
C <sub>max</sub> (Quetiapine)	1.61	1.27	2.04	3.52	2.96	4.19	2.19	1.73	2.76
C <sub>max</sub> (Quetiapine sulfoxide)	1.45	1.26	1.66	4.15	3.78	4.55	2.86	2.48	3.31
C <sub>max</sub> (7-hydroxy quetiapine)	1.26	1.02	1.55	0.16	0.13	0.18	0.12	0.10	0.15
C <sub>max</sub> (N-desalkyl quetiapine)	1.31	1.12	1.52	1.11	0.98	1.25	0.85	0.73	0.97
C <sub>min</sub> (Quetiapine)	1.37	0.95	1.96	0.19	0.13	0.26	0.14	0.10	0.18
C <sub>min</sub> (Quetiapine sulfoxide)	1.10	0.84	1.45	0.26	0.20	0.32	0.23	0.18	0.30
C <sub>min</sub> (7-hydroxy quetiapine)	1.02	0.76	1.38	0.01	0.01	0.02	0.01	0.01	0.02
C <sub>min</sub> (N-desalkyl quetiapine)	1.23	1.08	1.39	0.65	0.59	0.72	0.53	0.47	0.60

Table 5.1 Comparison of dose-normalized, weight-normalized AUC, Cmax and Cmin of quetiapine and 3 metabolites on combined data from children (10-12 years old) and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Children (10-12 years old)/Adults)			Children (10-12 years old)			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.65	0.53	0.80	676.76	550.13	832.53	1035.06	900.34	1189.93
AUC (Quetiapine sulfoxide)	0.89	0.79	1.00	950.04	851.17	1060.39	1069.14	986.39	1158.82
AUC (7-hydroxy quetiapine)	0.72	0.59	0.88	39.21	32.50	47.29	54.23	47.05	62.50
AUC (N-desalkyl quetiapine)	1.00	0.87	1.16	536.46	477.46	602.74	535.20	480.97	595.53
Cmax (Quetiapine)	0.72	0.60	0.85	187.38	159.52	220.11	261.76	232.12	295.19
Cmax (Quetiapine sulfoxide)	0.95	0.85	1.06	220.59	201.42	241.59	231.69	213.43	251.51
Cmax (7-hydroxy quetiapine)	0.76	0.62	0.94	8.29	7.01	9.82	10.88	9.34	12.69
Cmax (N-desalkyl quetiapine)	0.92	0.78	1.10	58.82	51.54	67.13	63.67	56.00	72.40
Cmin (Quetiapine)	0.49	0.35	0.67	9.93	6.92	14.26	20.37	16.49	25.16
Cmin (Quetiapine sulfoxide)	0.69	0.55	0.88	13.57	10.40	17.71	19.59	16.77	22.89
Cmin (7-hydroxy quetiapine)	0.54	0.42	0.69	0.79	0.60	1.04	1.47	1.25	1.74
Cmin (N-desalkyl quetiapine)	0.98	0.85	1.12	34.57	30.33	39.40	35.39	32.06	39.08

Table 5.2 Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites on combined data from adolescents (13-17 years old) and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Adolescents (13-17 years old)/Adults)			Adolescents (13-17 years old)			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.53	0.43	0.65	548.72	443.28	679.24	1035.06	900.34	1189.93
AUC (Quetiapine sulfoxide)	0.81	0.71	0.91	860.67	754.30	982.04	1069.14	986.39	1158.82
AUC (7-hydroxy quetiapine)	0.72	0.59	0.89	39.18	32.05	47.89	54.23	47.05	62.50
AUC (N-desalkyl quetiapine)	0.92	0.80	1.07	493.77	432.76	563.40	535.20	480.97	595.53
Cmax (Quetiapine)	0.52	0.43	0.63	135.84	108.59	169.93	261.76	232.12	295.19
Cmax (Quetiapine sulfoxide)	0.77	0.68	0.87	177.84	157.47	200.84	231.69	213.43	251.51
Cmax (7-hydroxy quetiapine)	0.71	0.57	0.88	7.69	6.29	9.40	10.88	9.34	12.69
Cmax (N-desalkyl quetiapine)	0.82	0.69	0.98	52.51	45.52	60.58	63.67	56.00	72.40
Cmin (Quetiapine)	0.42	0.31	0.57	8.48	6.20	11.60	20.37	16.49	25.16
Cmin (Quetiapine sulfoxide)	0.73	0.58	0.93	14.37	11.22	18.40	19.59	16.77	22.89
Cmin (7-hydroxy quetiapine)	0.61	0.47	0.79	0.90	0.67	1.20	1.47	1.25	1.74
Cmin (N-desalkyl quetiapine)	0.93	0.81	1.06	32.84	29.08	37.08	35.39	32.06	39.08

Table 5.3 Comparison of dose-normalized, weight-normalized AUC, Cmax, and Cmin of quetiapine and 3 metabolites on combined data from children (10-12 years old) and adolescents (13-17 years old)

Pharmacokinetic Parameter	Comparison (children/Adolescents)			Children (10-12 years old)			Adolescents (13-17 years old)		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (quetiapine)	1.23	0.97	1.57	676.76	550.13	832.53	548.72	443.28	679.24
AUC (quetiapine sulfoxide)	1.10	0.96	1.27	950.04	851.17	1060.39	860.67	754.30	982.04
AUC (7-hydroxy quetiapine)	1.00	0.80	1.25	39.21	32.50	47.29	39.18	32.05	47.89
AUC (N-desalkyl quetiapine)	1.09	0.94	1.25	536.46	477.46	602.74	493.77	432.76	563.40
Cmax (quetiapine)	1.38	1.10	1.72	187.38	159.52	220.11	135.84	108.59	169.93
Cmax (quetiapine sulfoxide)	1.24	1.10	1.40	220.59	201.42	241.59	177.84	157.47	200.84
Cmax (7-hydroxy quetiapine)	1.08	0.87	1.33	8.29	7.01	9.82	7.69	6.29	9.40
Cmax (N-desalkyl quetiapine)	1.12	0.96	1.31	58.82	51.54	67.13	52.51	45.52	60.58
Cmin (quetiapine)	1.17	0.79	1.73	9.93	6.92	14.26	8.48	6.20	11.60
Cmin (quetiapine sulfoxide)	0.94	0.70	1.27	13.57	10.40	17.71	14.37	11.22	18.40
Cmin (7-hydroxy quetiapine)	0.88	0.64	1.21	0.79	0.60	1.04	0.90	0.67	1.20
Cmin (N-desalkyl quetiapine)	1.05	0.91	1.22	34.57	30.33	39.40	32.84	29.08	37.08

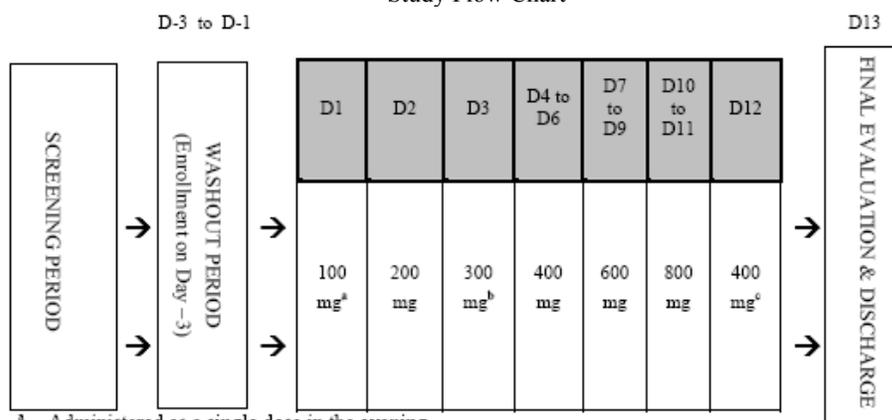
**Title (D1441C00130):** A Study to Characterize the Steady-State Pharmacokinetics and Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) in Adults with Selected Psychotic Disorders

**Background:** In response to a pediatric written request from the Agency, the sponsor originally designed a study to be conducted in subjects ages 10 to 17 years and in adults (ages 18 to 45). Adult subjects were included in order to provide concurrent PK data for quetiapine and its metabolites that could be compared with the PK data obtained in the pediatric and adolescent subjects. All subjects were to be titrated to steady-state doses using the same 10-day titration schedule, the safety and tolerability of which had not been previously studied. After a review of the original study protocol, the FDA requested that the titration schedule for 10- to 17-year-old subjects be extended to 11 days. As a result of this recommendation, the original study protocol was amended to include only pediatric and adolescent subjects (Study D1441C00028) using the 11-day titration schedule, and a separate study protocol (the present study) was developed for the adult subjects, retaining the 10-day titration schedule. The comparison of exposure to quetiapine and its metabolites in children 10 to 17 years of age to that seen in adults was conducted.

**Objectives:** The primary objective of this study was to characterize the steady-state PK of quetiapine administered as quetiapine tablets. The secondary objectives were: 1. Monitor the tolerability and safety of titrating doses of quetiapine, 2. Determine the dose-proportionality for quetiapine 3. Characterize the pharmacokinetics of 3 metabolites: quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine

**Study Design:** This was an open-label, multicenter, inpatient, steady-state, safety and tolerability study that characterized the pharmacokinetics of quetiapine in adults between 18 and 45 years of age. Steady-state PK design was chosen for the study because quetiapine is titrated based on tolerability until an adequate response is obtained. The study consisted of a 16-day/15-night inpatient stay at the clinical research center (CRC), including a 3-day pre-treatment washout period, a 12-day quetiapine treatment period, and 1 additional day for final evaluation. The following figure illustrates the design of the study. The 3-day washout period was included in order to wash subjects out from their current antipsychotic medications before beginning study drug administration on Day 1.

### Study Flow Chart



<sup>a</sup> Administered as a single dose in the evening.

<sup>b</sup> Administered as 100 mg in the morning and 200 mg in the evening.

<sup>c</sup> Administered as a single dose in the morning.

D Day.

Note: Doses shown are total daily doses administered in equally divided doses twice daily unless noted otherwise.

Subjects were dosed according to the following titration schedule:

#### Study medication titration schedule

Study day	Quetiapine dose and time of administration <sup>a</sup>
Day 1	100 mg at 2100 hr
Day 2	100 mg at 0900 hr and 100 mg at 2100 hr
Day 3	100 mg at 0900 hr and 200 mg at 2100 hr
Day 4	200 mg at 0900 hr and 200 mg at 2100 hr
Day 5	200 mg at 0900 hr and 200 mg at 2100 hr
Day 6	200 mg at 0900 hr and 200 mg at 2100 hr
Day 7	300 mg at 0900 hr and 300 mg at 2100 hr
Day 8	300 mg at 0900 hr and 300 mg at 2100 hr
Day 9	300 mg at 0900 hr and 300 mg at 2100 hr
Day 10	400 mg at 0900 hr and 400 mg at 2100 hr
Day 11	400 mg at 0900 hr and 400 mg at 2100 hr
Day 12	400 mg at 0900 hr

<sup>a</sup> Dose times are approximate.

Subjects were instructed not to chew or crush the tablets. On Days 6 and 12, subjects were administered their morning doses of quetiapine with 240 mL of water following an overnight fast of at least 8 hours. Subjects were provided standard meals no less than 4 hours after drug administration. Subjects were allowed water as required except for 1 hour before and after drug administration. Subjects were to remain in an upright or sitting position for at least 1 hour following dosing.

To verify that steady-state was achieved, plasma concentrations for the 200-mg morning dose were obtained before dosing on Days 5 and 6 and 12 hours after dosing on Day 6. Plasma concentrations for the 400-mg morning dose were obtained before dosing on Days 11 and 12 and 12 hours after dosing on Day 12. In order to characterize the PK profile of quetiapine and its metabolites, 2 mL serial blood sampling was done on Days 6 and 12 at 0, 0.25, 1, 1.5, 2, 3, 5, 8 and 12 hours post dose. In addition, 2 mL blood samples were taken at 16, 20 and 24 hours on Day 12 in order to calculate terminal half-life. A total urine collection was taken over the morning 12-hour, steady-state dosing interval on Days 6 and 12. Total urine PK samples were collected on Days 6 and 12, which included all urine collected following the morning dose and throughout the 12-hour dosing interval.

The details of the investigational product and any study treatment are given in the following table.

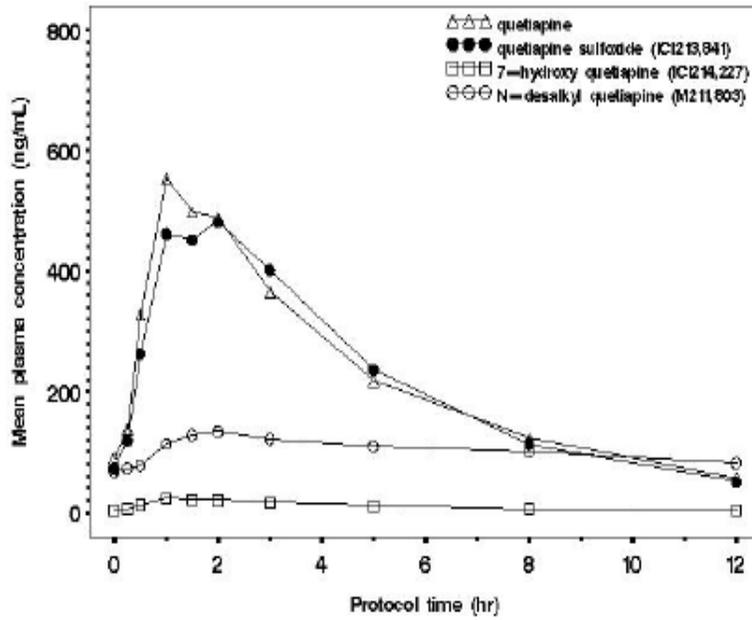
Details of investigational product				
Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch and lot number
Quetiapine	100-mg tablets	AstraZeneca	F12689	Batch No. 2000048407 Lot No. 6084C; Batch No. 2000053517 Lot No. 7511H

**Analytical Method:** The concentrations of quetiapine, quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine in plasma were determined by a validated method utilizing a liquid-liquid extraction from alkalized human EDTA plasma using ethyl acetate, followed by reverse-phase liquid chromatography and turbo ionspray ionization tandem mass spectrometry (LC/MS/MS). The method has a validated assay range of 0.500 to 500 ng/mL for all analytes, utilizing a 100 µL or 500 µL sample aliquot.

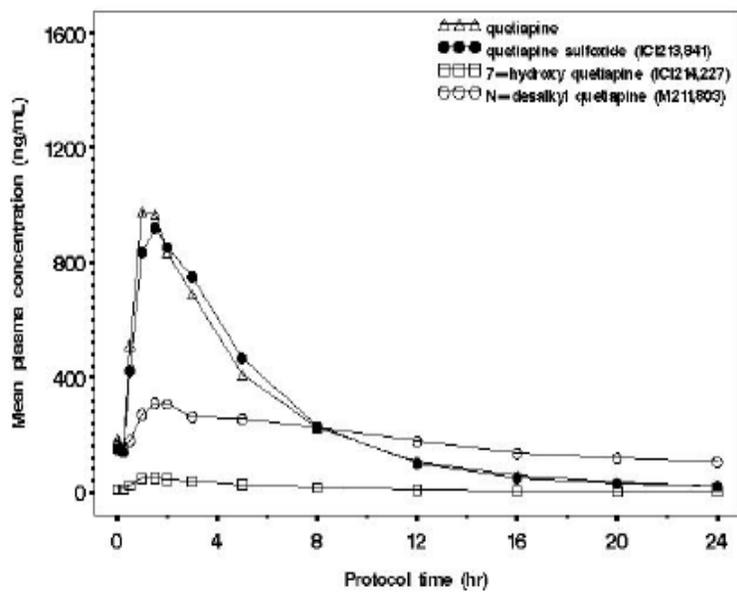
**Data Analysis:** Pharmacokinetic parameters for quetiapine and its metabolites were derived using non-compartmental methods from the plasma concentration versus time data. Quetiapine plasma concentration-time profiles were obtained on Day 6 (200-mg morning dose) and Day 12 (400-mg morning dose). The area under the plasma concentration versus time curve during the dosing interval at steady-state (AUC<sub>ss</sub>) and the maximum observed steady-state plasma concentration during a dosing interval (C<sub>ss,max</sub>) following the 200-mg and 400-mg morning doses on Days 6 and 12 were the primary variables.

**Results:** Mean plasma concentrations of quetiapine and 3 quetiapine metabolites are plotted over time in the following figures.

Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 6 (200-mg morning dose)



Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 12 (400-mg morning dose)



Descriptive statistics for quetiapine PK parameters are presented in the following table.

Pharmacokinetic parameters on Day 6 (200 mg) and Day 12 (400 mg) for quetiapine

PK parameter	Statistic	Day 6 (200-mg am dose) n=26	Day 12 (400-mg am dose) n=26
AUC <sub>∞</sub> (ng*hr/mL)	n <sup>a</sup>	25	25
	Geometric mean	2469.7	4508.9
	CV (%)	42.5	39.8
C <sub>∞,max</sub> (ng/mL)	n	26	26
	Geometric mean	660.3	1124.6
	CV (%)	41.9	31.9
t <sub>max</sub> (hr)	n	26	26
	Median	1.00	1.23
	Minimum	0.32	0.50
	Maximum	3.00	3.00
C <sub>∞,min</sub> (ng/mL)	n <sup>a</sup>	25	25
	Geometric mean	47.8	86.8
	CV (%)	72.1	65.9
CL/F (L/hr)	n <sup>a</sup>	25	25
	Mean	88.0	95.4
	SD	39.7	39.2
t <sub>1/2</sub> (hr)	n <sup>b</sup>	22	22
	Mean	3.34	5.10
	SD	0.62	0.91
Ael <sub>(m)</sub> (μg)	n <sup>c</sup>	19	19
	Mean	318.0	629.6
	SD	529.5	634.2
Fu (%)	n <sup>c</sup>	19	19
	Mean	0.159	0.157
	SD	0.265	0.159
CL <sub>R</sub> (L/hr)	n <sup>d</sup>	18	18
	Mean	0.126	0.134
	SD	0.180	0.099

<sup>a</sup> Excludes 1 subject for whom no 12-hr sample on Day 6 was obtained.

<sup>b</sup> Excludes 4 subjects for whom the parameter could not be calculated.

<sup>c</sup> Excludes 7 subjects for whom the parameter could not be calculated.

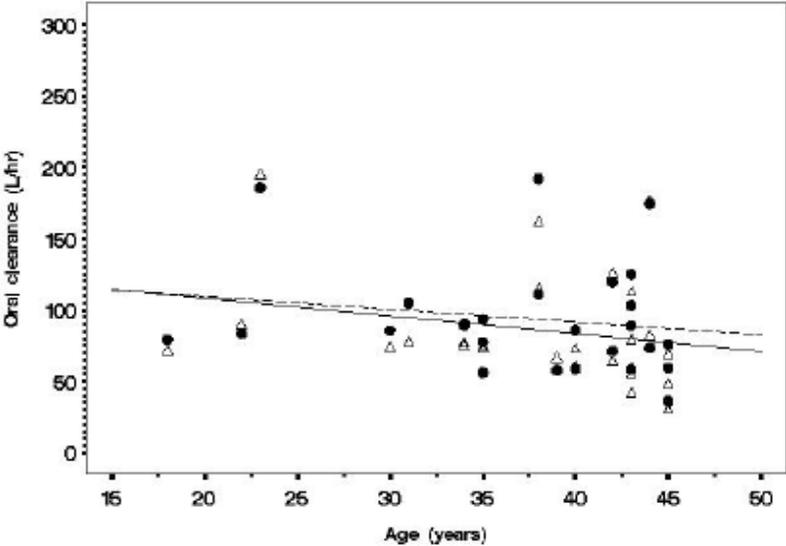
<sup>d</sup> Excludes 8 subjects for whom the parameter could not be calculated.

Ael<sub>(m)</sub> amount of metabolite eliminated. am morning. AUC<sub>∞</sub> area under the curve at steady-state. CL/F apparent oral clearance. CV coefficient of variation. CL<sub>R</sub> renal clearance from plasma. C<sub>∞,max</sub> maximum plasma concentration at steady-state. C<sub>∞,min</sub> minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t<sub>max</sub> time of maximum plasma concentration. t<sub>1/2</sub> terminal elimination half-life.

7

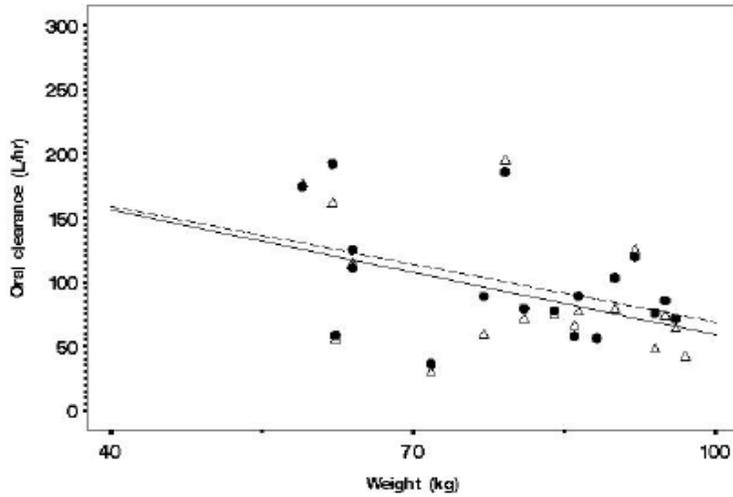
A scatter plot of CL/F by age, weight and body mass index are provided in the following figures.

Scatter plot of oral clearance (CL/F) of quetiapine by age for Day 6 (200-mg morning dose) and Day 12 (400-morning dose)

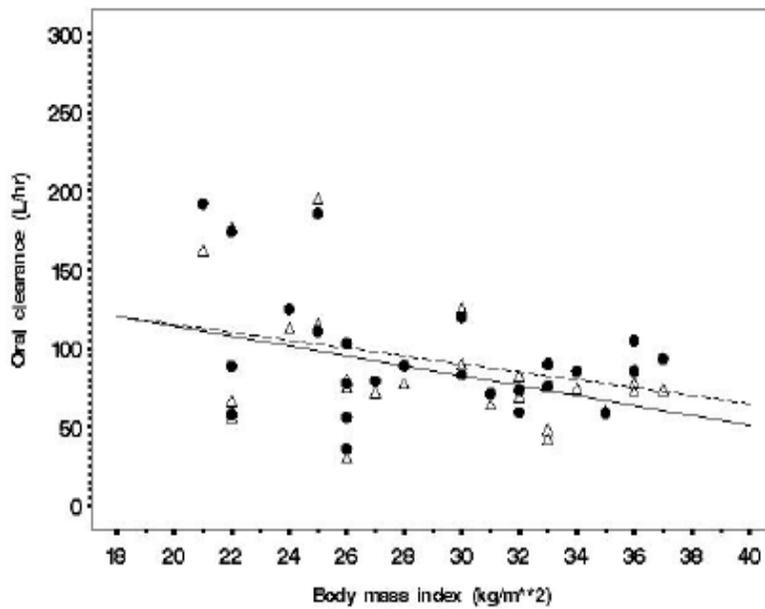


Triangle: Observed values for Day 6  
Dot: Observed values for Day 12  
Solid line: Linear regression for Day 6  
Dash line: Linear regression for Day 12

Scatter plot of oral clearance (CL/F) of quetiapine by weight for Day 6 (200-mg) and Day 12 (400-mg morning dose)



Scatter plot of oral clearance (CL/F) of quetiapine by body mass index for Day 6 (200-mg) and Day 12 (400-mg morning dose)



The regression lines showed that CL/F tended to decrease with age, weight and body mass index (BMI). There was great variability in the data.

Pharmacokinetic parameters at steady-state are summarized for the 3 metabolites, quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine, are provided in the following tables.

Pharmacokinetic parameters for quetiapine sulfoxide on day 6 (200 mg) and day 12 (400 mg)

PK parameter	Statistic	Day 6 (200-mg am dose) n=26	Day 12 (400-mg am dose) n=26
AUC <sub>w</sub> (ng*hr/mL)	n <sup>a</sup>	25	25
	Geometric mean	2547.3	4889.5
	CV (%)	28.1	24.8
C <sub>ss,max</sub> (ng/mL)	n	26	26
	Geometric mean	580.5	1006.2
	CV (%)	33.8	26.4
t <sub>max</sub> (hr)	n	26	26
	Median	1.26	1.50
	Minimum	0.32	0.50
	Maximum	3.00	5.00
C <sub>ss,min</sub> (ng/mL)	n <sup>a</sup>	25	25
	Geometric mean	46.1	90.4
	CV (%)	52.4	51.9
t <sub>1/2</sub> (hr)	n <sup>b</sup>	21	21
	Mean	3.05	4.84
	SD	0.48	0.83
Ael <sub>(m)</sub> (μg)	n <sup>c</sup>	19	19
	Mean	1748.2	3754.2
	SD	1349.2	1495.3
Fu (%)	n <sup>c</sup>	19	19
	Mean	0.839	0.901
	SD	0.648	0.359
CL <sub>R</sub> (L/hr)	n <sup>d</sup>	18	18
	Mean	0.706	0.809
	SD	0.473	0.324

<sup>a</sup> Excludes 1 subject for whom no 12-hr sample on Day 6 was obtained.

<sup>b</sup> Excludes 5 subjects for whom the parameter could not be calculated.

<sup>c</sup> Excludes 7 subjects for whom the parameter could not be calculated.

<sup>d</sup> Excludes 8 subjects for whom the parameter could not be calculated.

Ael<sub>(m)</sub> amount of metabolite eliminated, am morning. AUC<sub>w</sub> area under the curve at steady-state. CL<sub>R</sub> renal clearance from plasma. C<sub>ss,max</sub> maximum plasma concentration at steady-state. C<sub>ss,min</sub> minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t<sub>max</sub> time of maximum plasma concentration. t<sub>1/2</sub> terminal elimination half-life.

Pharmacokinetic parameters for 7-hydroxy quetiapine on Day6 (200 mg) and Day 12 (400 mg)

PK parameter	Statistic	Day 6 (200-mg am dose) n=26	Day 12 (400-mg am dose) n=26
AUC <sub>0-∞</sub> (ng*hr/mL)	n <sup>a</sup>	25	25
	Geometric mean	123.3	272.7
	CV (%)	51.7	45.7
C <sub>max</sub> (ng/mL)	n	26	26
	Geometric mean	24.5	52.7
	CV (%)	64.1	57.0
t <sub>max</sub> (hr)	n	26	26
	Median	1.01	1.23
	Minimum	0.32	0.50
	Maximum	3.0	3.0
C <sub>min</sub> (ng/mL)	n <sup>a</sup>	25	25
	Geometric mean	3.41	7.30
	CV (%)	56.2	59.2
t <sub>1/2</sub> (hr)	n <sup>b</sup>	15	15
	Mean	3.95	5.58
	SD	0.65	0.94
Ael <sub>(ex)</sub> (μg)	n <sup>c</sup>	19	19
	Mean	169.0	392.1
	SD	129.4	209.9
Fu (%)	n <sup>d</sup>	19	19
	Mean	0.081	0.094
	SD	0.062	0.050
CL <sub>R</sub> (L/hr)	n <sup>d</sup>	18	18
	Mean	1.313	1.386
	SD	0.560	0.432

<sup>a</sup> Excludes 1 subject for whom no 12-hr sample on Day 6 was obtained.

<sup>b</sup> Excludes 11 subjects for whom the parameter could not be calculated.

<sup>c</sup> Excludes 7 subjects for whom the parameter could not be calculated.

<sup>d</sup> Excludes 8 subjects for whom the parameter could not be calculated.

Ael<sub>(ex)</sub> amount of metabolite eliminated, am morning, AUC<sub>0-∞</sub> area under the curve at steady-state, CL<sub>R</sub> renal clearance from plasma, C<sub>0,max</sub> maximum plasma concentration at steady-state, C<sub>0,min</sub> minimum plasma concentration at steady-state, Fu mole fraction (percent) of dose excreted in the urine, SD standard deviation, t<sub>max</sub> time of maximum plasma concentration, t<sub>1/2</sub> terminal elimination half-life.

Pharmacokinetic parameters for N-desalkyl quetiapine on Day 6 (200 mg) and Day 12 (400 mg)

PK parameter <sup>a</sup>	Statistic	Day 6 (200-mg am dose) n=26	Day 12 (400-mg am dose) n=26
AUC <sub>0-∞</sub> (ng <sup>h</sup> /mL)	n <sup>b</sup>	24	24
	Geometric mean	1154.7	2585.4
	CV (%)	33.9	35.1
C <sub>max</sub> (ng/mL)	n	26	26
	Geometric mean	144.1	306.2
	CV (%)	44.9	49.6
t <sub>max</sub> (hr)	n	26	26
	Median	2.00	2.00
	Minimum	0.25	1.00
	Maximum	8.00	8.00
C <sub>min</sub> (ng/mL)	n <sup>b</sup>	24	24
	Geometric mean	77.9	169.0
	CV (%)	32.2	30.3
Ael <sub>(m)</sub> (μg)	n <sup>c</sup>	19	19
	Mean	3555.4	7930.5
	SD	2532.8	4933.5
Fu (%)	n <sup>c</sup>	19	19
	Mean	2.308	2.574
	SD	1.644	1.601
CL <sub>R</sub> (L/hr)	n <sup>d</sup>	17	17
	Mean	2.511	2.473
	SD	1.686	1.328

<sup>a</sup> t<sub>1/2</sub> results are omitted from this table as there were only 3 subjects who provided data on both Days 6 and 12.

<sup>b</sup> Excludes 1 subject for whom no 12-hr sample on Day 6 was obtained and 1 subject for whom the parameter could not be calculated.

<sup>c</sup> Excludes 7 subjects for whom the parameter could not be calculated.

<sup>d</sup> Excludes 9 subjects for whom the parameter could not be calculated.

Ael<sub>(m)</sub> amount of metabolite eliminated. am morning. AUC<sub>0-∞</sub> area under the curve at steady-state. CL<sub>R</sub> renal clearance from plasma. C<sub>max,ss</sub> maximum plasma concentration at steady-state. C<sub>min,ss</sub> minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. NA not applicable. SD standard deviation. t<sub>max</sub> time of maximum plasma concentration. t<sub>1/2</sub> terminal elimination half-life.

## Pharmacokinetic summary

Quetiapine was rapidly absorbed with a T<sub>max</sub> between 1 and 1.2 hours after dosing, and had a t<sub>1/2</sub> of approximately 5 hours. Two of the metabolites, quetiapine sulfoxide and 7-hydroxy quetiapine, had estimates of t<sub>1/2</sub> similar to quetiapine. The N-desalkyl quetiapine metabolite had a longer t<sub>1/2</sub> than quetiapine. Estimates of the t<sub>1/2</sub> for N-desalkyl quetiapine ranged from 7.6 to 20.8 hours. In terms of in vivo exposure, the rank order of exposure with respect to AUC<sub>ss</sub> was: quetiapine sulfoxide≈quetiapine>N-desalkyl quetiapine>7-hydroxy quetiapine. The rank order of in vivo exposure with respect to C<sub>ss,max</sub> was: quetiapine≈quetiapine sulfoxide>N-desalkyl quetiapine>7-hydroxy quetiapine. Urinary excretion of quetiapine and its metabolites appeared to be minor.

## Summary of Safety

The sponsor reported that quetiapine was well tolerated in this study population. The sponsor reported that one subject was withdrawn from the study on Day 3 as a result of severe agitation that was considered unrelated to the study treatment. Dizziness was the most frequently occurring AE during study treatment (13 of 29 subjects). The majority of occurrences of dizziness were considered treatment related. Dizziness tended to occur shortly after study treatment began, was typically rated by the investigators as mild in intensity, and was transient. Slightly over one-half of the subjects reporting dizziness had accompanying vital signs changes consistent with orthostatic hypotension. Other frequently occurring AEs included anxiety, lethargy, dry mouth, and insomnia. The majority of these events were rated by the investigators as mild in intensity. The majority of occurrences of lethargy and dry mouth were considered treatment related.

**Reviewer Summary:** *The steady-state pharmacokinetics of quetiapine and 3 metabolites were characterized in adults from 18 to 45 years of age with primary diagnoses of schizophrenia, schizoaffective disorder, or bipolar I disorder. The rank order of exposure with respect to AUC<sub>ss</sub> was: quetiapine sulfoxide≈quetiapine>N-desalkyl quetiapine>7-hydroxy quetiapine. The rank order of in vivo exposure with respect to C<sub>ss,max</sub> was: quetiapine≈quetiapine sulfoxide>N-desalkyl quetiapine>7-hydroxy quetiapine. Exposure (AUC<sub>ss</sub>, C<sub>max</sub>) to quetiapine tended to increase with an increase in age and weight. Urinary excretion of quetiapine and its metabolites appeared to be minor.*

Appendix

Table 11.2.1.1 Summary statistics for guastipina pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter	Study Day		
	Day 6 (N=26)	Day 12 (N=26)	
AUC (ng*hr/mL)	N	25	25
	Mean	2667.551	4831.602
	SD	1101.697	1881.882
	Minimum	1025.28	2083.33
	Median	2666.94	4661.12
	Maximum	6516.77	10986.38
	Geometric Mean	2469.650	4508.947
	CV(%)	42.470	39.768
Cmax (ng/nL)	N	26	26
	Mean	708.808	1176.808
	SD	254.859	355.749
	Minimum	231.00	686.00
	Median	639.00	1215.00
	Maximum	1220.00	1990.00
	Geometric Mean	660.266	1124.564
	CV(%)	41.942	31.909
tmax (hr)	N	26	26
	Minimum	0.32	0.50
	Median	1.00	1.23
	Maximum	3.00	3.00

Table 11.2.1.1 Summary statistics for guanfacine pharmacokinetic parameter estimates  
- PK evaluable subjects

Pharmacokinetic Parameter	Study Day		
	Day 6 (N=26)	Day 12 (N=26)	
C <sub>min</sub> (ng/mL)	N	25	25
	Mean	57.604	101.664
	SD	34.866	58.360
	Minimum	13.70	19.30
	Median	52.20	89.60
	Maximum	155.00	298.00
	Geometric Mean	47.849	86.834
	CV(%)	72.146	65.875
	CL/F (L/hr)	N	25
Mean		88.012	95.362
SD		39.747	39.205
Minimum		30.69	36.41
Median		74.99	85.82
Maximum		195.07	192.00
Geometric Mean		80.983	88.713
CV(%)		42.470	39.768
t <sub>1/2</sub> (hr)		N	22
	Mean	3.341	5.097
	SD	0.617	0.910
	Minimum	2.53	3.77

Table 11.2.1.2 Summary statistics for quetiapine sulfoxide (ICI213,841) pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter	Study Day		
	Day 6 (N=26)	Day 12 (N=26)	
AUC (ng*hr/mL)	N	25	25
	Mean	2642.927	5031.802
	SD	755.389	1264.530
	Minimum	1418.05	2471.88
	Median	2523.88	4730.36
	Maximum	4577.72	8675.72
	Geometric Mean	2547.334	4889.533
	CV(%)	28.076	24.781
Cmax (ng/mL)	N	26	26
	Mean	610.000	1037.077
	SD	189.920	248.792
	Minimum	272.00	438.00
	Median	572.50	997.50
	Maximum	1080.00	1580.00
	Geometric Mean	580.529	1006.217
	CV(%)	33.847	26.426
tmax (hr)	N	26	26
	Minimum	0.32	0.50
	Median	1.26	1.50
	Maximum	3.00	5.00

Table 11.2.1.2 Summary statistics for quetiapine sulfoxide (ICI213,841) pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter	Study Day		
	Day 6 (N=26)	Day 12 (N=26)	
C <sub>min</sub> (ng/mL)	N	25	25
	Mean	51.652	101.216
	SD	26.251	50.143
	Minimum	16.70	37.70
	Median	47.10	96.00
	Maximum	137.00	234.00
	Geometric Mean	46.077	90.448
	CV(%)	52.374	51.859
	t <sub>1/2</sub> (hr)	N	21
Mean		3.054	4.836
SD		0.478	0.832
Minimum		2.16	3.22
Median		3.07	4.95
Maximum		3.96	6.51
Lambda <sub>z</sub> (hr <sup>-1</sup> )	N	21	21
	Mean	0.233	0.148
	SD	0.037	0.027
	Minimum	0.18	0.11
	Median	0.23	0.14
	Maximum	0.32	0.22

Table 11.2.1.3 Summary statistics for 7-hydroxy quetiapine (ICI214,227) pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter	Study Day		
		Day 6 (N=26)	Day 12 (N=26)
AUC (ng*hr/mL)	N	25	25
	Mean	136.688	295.886
	SD	59.378	112.367
	Minimum	35.82	90.74
	Median	135.41	303.74
	Maximum	239.59	519.35
	Geometric Mean	123.273	272.714
	CV(%)	51.787	48.698
C <sub>max</sub> (ng/mL)	N	26	26
	Mean	28.422	59.119
	SD	14.712	25.646
	Minimum	7.55	15.90
	Median	25.10	56.35
	Maximum	60.00	101.00
	Geometric Mean	24.479	52.661
	CV(%)	64.058	57.028
t <sub>max</sub> (hr)	N	26	26
	Minimum	0.32	0.50
	Median	1.01	1.23
	Maximum	3.00	3.00

Table 11.2.1.3 Summary statistics for 7-hydroxy quetiapine (ICI214,227) pharmacokinetic parameter estimates  
- PK evaluable subjects

Pharmacokinetic Parameter	Study Day		
	Day 6 (N=26)	Day 12 (N=26)	
C <sub>min</sub> (ng/mL)	N	25	25
	Mean	3.859	8.305
	SD	1.924	3.979
	Minimum	1.12	2.28
	Median	3.79	7.71
	Maximum	8.77	15.30
	Geometric Mean	3.411	7.295
	CV(%)	56.158	59.234
Lambda <sub>z</sub> (hr <sup>-1</sup> )	N	15	15
	Mean	0.181	0.127
	SD	0.030	0.023
	Minimum	0.13	0.09
	Median	0.18	0.13
	Maximum	0.24	0.18
	Geometric Mean	0.178	0.126
	CV(%)	16.837	17.671
t <sub>1/2</sub> (hr-1)	N	15	15
	Mean	3.949	5.581
	SD	0.645	0.943
	Minimum	2.67	3.75

Table 11.2.1.4 Summary statistics for N-desalkyl quetiapine (M211,803) pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter	Study Day		
	Day 6 (N=26)	Day 12 (N=26)	
AUC (ng*hr/mL)	N	24	24
	Mean	1214.005	2723.560
	SD	379.854	848.683
	Minimum	602.61	1263.54
	Median	1151.78	2665.03
	Maximum	1986.37	4057.61
	Geometric Mean	1154.690	2585.400
	CV(%)	33.933	35.075
Cmax (ng/mL)	N	26	26
	Mean	156.350	338.731
	SD	60.395	151.242
	Minimum	62.70	126.00
	Median	150.50	306.50
	Maximum	287.00	710.00
	Geometric Mean	144.107	306.160
	CV(%)	44.877	49.604
tmax (hr)	N	26	26
	Minimum	0.25	1.00
	Median	2.00	2.00
	Maximum	8.00	8.00

Figure 11.2.1.1.1 Individual values of AUC of quetiapine versus quetiapine dose

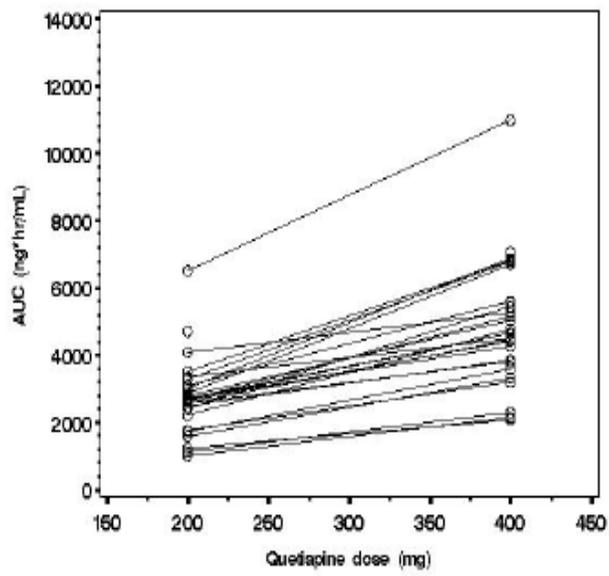
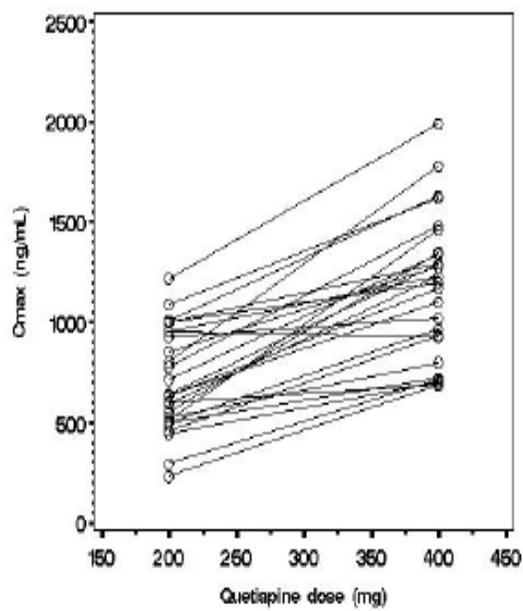


Figure 11.2.1.1.2 Individual values of C<sub>max</sub> of quetiapine versus quetiapine dose



4.3.

## OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

### 8 SUMMARY OF FINDINGS

#### 8.1 Key Review Questions

The purpose of this review is to address the following key questions.

##### 8.1.1 Does quietapine prolong QTc interval in children and adolescents at the proposed clinical doses?

Quietapine does not appear to prolong QTc interval in children and adolescents at the proposed clinical doses. The potential for QTc prolongation at the proposed doses was evaluated by using the quietapine concentration-QTcF relationship derived from a thorough QT study in healthy adults. Assuming the concentration-QT relationships are similar between the pediatric patients and healthy adults, the model predicted mean placebo-corrected, baseline-adjusted QTc ( $\Delta\Delta\text{QTc}$ ) intervals are less than 10 ms (**Table 2**~~Error! Reference source not found.~~) following the highest dose (i.e. 400 mg BID) tested in the two pivotal pediatric studies (Study D1441C00112 and Study D1441C00149). In addition, the largest mean QTc interval change from baseline ( $\Delta\text{QTcF}$ ) observed in the clinical trials was around 2 ms (Table 3). No patients had QTcF values larger than 500 ms or  $\Delta\text{QTcF}$  greater than 60 ms.

**Table 2: Model Predicted  $\Delta\Delta\text{QTcF}$  Values**

Daily Dose (mg/day)	Dose (mg)	Dosing	$C_{\text{max}}$ (ng/mL)	Predicted QTcF (90% CI) (ms)
400	200	BID	520.9	5.4 (3.6 - 7.1)
600	300	BID	1023.6	6.8 (4.9 - 8.7)
800	400	BID	1113.4	6.9 (5.0 - 8.9)

The two pivotal pediatric studies (Study D1441C00112 and Study D1441C00149) had slightly different results for  $\Delta\text{QTc}$  following quietapine treatment. As shown in Table 3, a larger (i.e., approximately 2 ms)  $\Delta\text{QTcF}$  was seen in quietapine treated groups as compared to the placebo group in Study D1441C00112. However,  $\Delta\text{QTcF}$  for quietapine treated groups (e.g. -1.1 ms in 600 mg/day dose group) was similar to the placebo group (i.e. -1.2 ms in placebo group) in Study D1441C00149.

Suboptimal ECG sampling may lead to the difference in QTc results. Firstly, it has been found that the change in QTc interval is driven by drug concentration. If the ECGs were not taken at the same time post-dose between the two trials, the results may be different. Secondly, diurnal effect has been shown to affect QTc intervals. If the ECGs were not collected in time-matched fashion between the placebo group and treatment group or between the final visit and baseline visit, the results can be variable. Thirdly, QTc intervals may change over weeks. In the two studies, the baseline values were collected either 3 weeks or 6 weeks prior to the final visit. Different lag time between the ECGs observed at baseline and at the final visit may lead to different results. Furthermore, the QTc itself is highly variable, especially when ECGs were not taken in triplicates.

**Table 3 Summary of the QTcF change from Baseline Values**

Study		D1441C00112	D1441C00149
Patients		schizophrenia	Bipolar I mania
Treatment	Age	13 ~ 17	10 ~ 17
Placebo	Mean (SD)	-2.1 (18.1)	-1.2 (17.6)
	N	71	81
400 mg/day	Mean (SD)	1.96 (16.2)	-0.11 (16.1)
	N	72	94
600 mg/ day	Mean (SD)	-	-1.1 (16.8)
	N	-	98
800 mg/day	Mean (SD)	1.96 (18.1)	-
	N	73	-

## 9 PERTINENT REGULATORY BACKGROUND

Quetiapine (Seroquel®) has been approved as monotherapy for the treatment of depressive episodes associated with bipolar disorder in adults. It has also been approved as either monotherapy or adjunctive therapy for the treatment of the acute episodes of bipolar I disorder in adults. Additionally, it is used for the maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or divalproex in adults.

The sponsor provided the pediatric study reports in the current submission to fulfill the pediatric Written Request originated on 11 February 2003, and subsequently amended on 7 May 2004 and 3 February 2005. The sponsor is seeking an additional six-month marketing exclusivity and the indication for the treatment of acute maniac episodes associated with bipolar I disorder in children and adolescents (10 – 17 years) and schizophrenia in adolescent (13 – 17 years).

## 10 RESULTS OF SPONSOR' S ANALYSIS

Study D1441C00112 was a 6-week, multicenter, double-blind, parallel-group, randomized, placebo-controlled study to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 800 mg/day) with that of placebo in patients aged 13 to 17 years with schizophrenia. The double-blind study was preceded by a medication washout period of 1 to 28 days based on the current medications at screening. Of the 268 patients enrolled in this study, 222 were randomly assigned to study treatment. With 73 patients in the 400 mg/day quetiapine group, 74 patients in the 800 mg/day quetiapine group, and 75 patients in the placebo group, the randomization goals were considered to be adequately satisfied. Treatment began with a 50-mg

dose on the evening of Day 1. The dose was escalated daily in increments of 100 mg thereafter, to reach a target fixed dose of 400 mg/day by Day 5 or 800 mg/day by Day 9, according to randomized treatment assignment. The overall treatment duration was 6 weeks. Twelve-lead ECGs were performed at screening and on Day 42 (or withdrawal). QTc intervals were calculated using the Fridericia formula. Based on the clinical observation, the QT results were shown in Table 4.

Study D1441C00149 was a 3-week, multicenter, double-blind, parallel-group, randomized, placebo-controlled study to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 600 mg/day) and placebo, given in divided doses (either twice daily [bid] or three times daily [tid], per the judgment of the investigator), in patients aged 10 to 17 years with Bipolar I mania. Of the 393 patients screened for this study, 284 were randomly assigned to study treatment. With 95 patients in the 400 mg quetiapine group, 98 patients in the 600 mg quetiapine group, and 91 patients in the placebo group, the randomization goals were considered to be adequately satisfied.

Treatment began with a 50 mg dose on the evening of Day 1. On Day 2, the dose was increased to 50 mg twice daily (i.e., 100 mg/day). Thereafter, the dose was escalated in 100 mg increments daily to reach a target of 400 mg/day by Day 5 or 600 mg/day by Day 7, according to randomized treatment assignment. Placebo to match 25 mg and 100 mg quetiapine tablets was administered orally in blinded fashion, according to randomized treatment assignment. The overall treatment duration was 21 days (3 weeks). QTc intervals were calculated using the Fridericia formula. ECGs were administered at screening period and by the end of the treatment. Based on the clinical observation, the QT results were demonstrated in Table 6.

*Reviewer's Comments: The reviewer performed additional analysis to further evaluate the quetiapine's QTc effect. There are several factors which may contribute to the inconsistent results. Firstly, the mean QTcF interval change from baseline following various doses of quetiapine is not expected to be large. Assuming the concentration-QT relationships are similar between the pediatric patients and healthy adults, the model predicted mean placebo-corrected, baseline-adjusted QTc ( $\Delta\Delta QTc$ ) intervals were less than 7 ms. Secondly, it has been found that the change in QTc interval is driven by drug concentration. If the ECGs were not taken at the same time post-dose between the two trials, the results may be different. Thirdly, diurnal effect has been shown to affect QTc intervals. If the ECGs were not collected in time-matched fashion between the placebo group and treatment group or between the final visit and baseline visit, the results can be variable. Fourthly, QTc intervals may change over weeks. In the two studies, the baseline values were collected either 3 weeks or 6 weeks prior to the final visit. Different lag time between the ECGs observed at baseline and at the final visit may lead to inconsistent results. Furthermore, the QTc itself is highly variable, especially when it is measured in triplicates .*

**Table 4 Vital Signs and Change from Baseline to the Final Visit  
(Study D1441C00112)**

	Quetiapine 400 mg/day (N=73)			Quetiapine 800 mg/day (N=74)			Placebo (N=75)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
<b>Vital signs</b>									
Supine pulse (bpm)	73	6.0	12.32	74	3.9	12.16	73	-1.4	11.31
Supine systolic BP (mmHg)	73	2.0	10.30	74	1.0	9.72	73	-1.6	7.41
Supine diastolic BP (mmHg)	73	1.3	8.37	74	0.2	12.37	73	0.1	8.48
Standing pulse (bpm)	73	6.3	13.12	74	2.2	17.08	73	-2.5	13.14
Standing systolic BP (mmHg)	73	2.3	10.78	74	-0.4	10.26	73	-1.7	9.10
Standing diastolic BP (mmHg)	73	2.1	8.65	74	1.1	10.24	73	-1.2	7.68
Temperature (°C)	73	0.01	0.562	73	0.05	0.773	73	-0.03	0.563
Weight (kg)	73	1.9	2.47	73	1.5	2.63	73	-0.1	2.84
Height (cm)	73	0.3	0.81	73	0.3	0.88	73	0.2	0.69
<b>ECG</b>									
Heart rate (bpm)	64	3.78	16.52	64	11.16	14.88	65	-3.32	12.04
RR interval (msec)	64	-42.06	148.30	64	-101.09	127.59	65	33.23	128.34
PR interval (msec)	64	-1.97	32.10	64	2.77	12.97	65	1.12	12.51
QRS interval (msec)	64	0.30	8.54	64	-0.09	6.11	65	-0.25	6.38
QT interval (msec)	64	-4.88	26.39	64	-12.97	28.46	65	2.63	26.46
Fridericia's corrected QTc interval (msec)	64	1.41	16.47	64	3.13	17.48	65	-2.55	18.41
Bazett's corrected QTc interval (msec)	64	5.08	22.45	64	12.22	18.86	65	-5.57	20.93

**Table 5 Vital Signs and Change from Baseline to the Final Visit  
(Study D1441C00112)**

	Quetiapine 400 mg (N=95)			Quetiapine 600 mg (N=98)			Placebo (N=90)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
<b>ECG</b>									
Heart rate (bpm)	90	12.76	12.37	87	13.36	15.52	79	-1.73	11.64
RR interval (msec)	90	-121.24	123.38	87	-136.11	165.14	79	18.20	138.03
PR interval (msec)	90	0.62	14.12	88	-0.76	13.72	81	-0.23	13.88
QRS interval (msec)	90	-0.98	6.31	87	-0.32	5.99	79	1.33	6.33
QT interval (msec)	90	-19.84	23.61	87	-22.84	24.70	79	1.39	27.65
Fridericia's corrected QTc interval (msec)	90	-0.80	15.90	87	-2.41	16.42	79	-1.68	17.57
Bazett's corrected QTc interval (msec)	90	10.22	19.89	87	9.16	24.29	79	-3.43	19.72

## 11 REVIEWER' S ANALYSIS

### 11.1 Introduction

The reviewer performed additional analysis to evaluate the QT interval change following quetiapine treatment.

### 11.2 Objective

Analysis objective was to evaluate quetiapine's QTc effect in pediatrics.

### 11.3 Methods

We compared the QTc interval change from the baseline in the quetiapine treatment group with the placebo group by the final day of the treatment.

#### 11.3.1 Data Sets

Data sets used are summarized in Table 6.

**Table 6. Analysis Data Sets**

Study Number	Name	Link to EDR
Study 112	Ecg_e xpt	\\cdsnas\pharmacometrics\
Study 149	Ecg_e xpt	\\cdsnas\pharmacometrics\

#### 11.3.2 Software

The analysis was conducted by using S\_Plus (Version 7.0, Insightful, Inc.).

## 11.4 Results

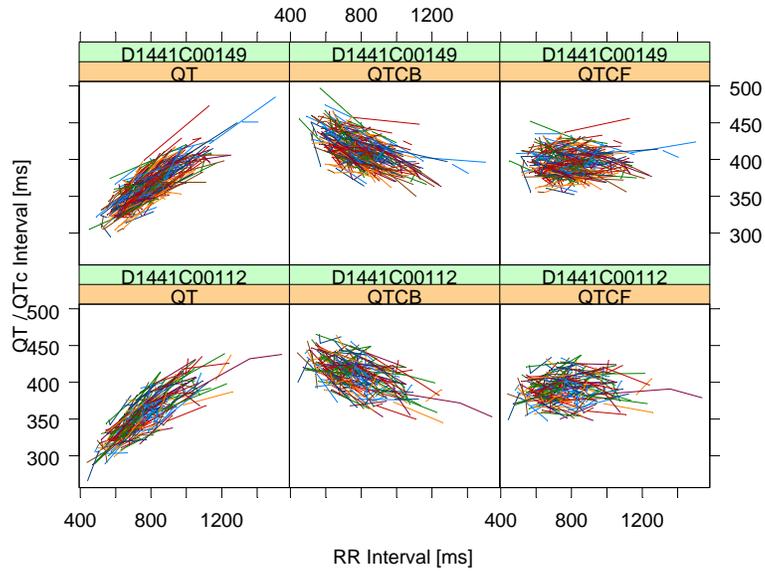
A scrutiny of the data indicated minimal QTcF change from baseline from the two pivotal trials (

Table 7).

**The observed QT-RR interval relationship was presented in**

Figure 1 together with the Bazett's (QTcB) and Fridericia (QTcF) stratified by different study (patient population). It appeared that QTcF was the best correction method to remove the heart rate effect. Therefore it was chosen for further analyses.

**Figure 1 QT, QTcB, QTcF, and QTcS vs. RR, by Study (or Patient Population)  
(Each Subject's Data Points are Connected with a Line)**



Note:

Study D1441C00112 is conducted in patients aged 13 to aged 13 to 17 years with schizophrenia

Study D1441C00149 is conducted in patients aged 10 to 17 years with Bipolar I mania

**Table 7 Summary of the Number of Patients with different QTcF change from Baseline**

Study	Dose Group	Dosing	Total Number of patients	Number of patients		
				dQTcF > 30 ms	dQTcF > 60 ms	QTcF > 500 ms
D1441C00112	Placebo	0	68	2	0	0
D1441C00112	400 mg / day	200 mg BID	70	2	0	0

D1441C00112	800 mg / day	300 mg BID	72	2	0	0
D1441C00149	Placebo	0	80	1	0	0
D1441C00149	400 mg / day	200 mg BID	92	1	0	0
D1441C00149	600 mg / day	400 mg BID	87	5	0	0

We compared the QTc change from the baseline in different dose groups and the results were shown in Table 8. It appears that QTc values are inconsistent between the two pivotal trials (Study D1441C00112 and Study D1441C00149). As shown in Table 8, a larger (i.e., approximately 4 ms)  $\Delta$ QTcF was seen in quietapine treated groups as compared to the placebo group in Study D1441C00112. However,  $\Delta$ QTcF for quietapine treated groups was similar to the placebo group in Study D1441C00149.

**Table 8: Summary of the QTcF change from Baseline Values**

Study		D1441C00112	D1441C00149
Patients		schizophrenia	Bipolar I mania
Treatment	Age	13 ~ 17	10 ~ 17
Placebo	Mean (SD)	-2.1 (18.1)	-1.2 (17.6)
	N	71	81
400 mg/ day	Mean (SD)	1.96 (16.2)	-0.11 (16.1)
	N	72	94
600 mg/ day	Mean (SD)	-	-1.1 (16.8)
	N	-	98
800 mg/ day	Mean (SD)	1.96 (18.1)	-
	N	73	-

In an effort to understand the different QTc results between the two pivotal studies. We applied the concentration-QTc model derived from the thorough QT study in healthy adults. (Please refer to QT-IRT report for NDA 21999: paliperidone). Briefly, this thorough QTc study was a placebo- and active-controlled, 3-arm parallel study. All subjects underwent a 6-day placebo washout phase, and then received 1-day of open-label moxifloxacin treatment. They were then randomized 2:2:1 to 10 days of double-blind treatment of INVEGA™, SEROQUEL®, or placebo ( ). The 4 treatment arms were listed as the following:

- Moxifloxacin: 400 mg (Day 1)
- Placebo: Day 2-11
- Quetiapine IR : 100 mg bid (Day 2), 200 mg bid (Day 3), 300 mg bid (Day 4), and 400 mg bid (Day 5-11)
- Paliperidone ER: 12 mg qd (Day 2-5) and 18 mg qd (Day 8-11)

Blood samples and ECGs were collected at various time points (Table 9).

**Table 9 Highlights of Schedule of Intervention**

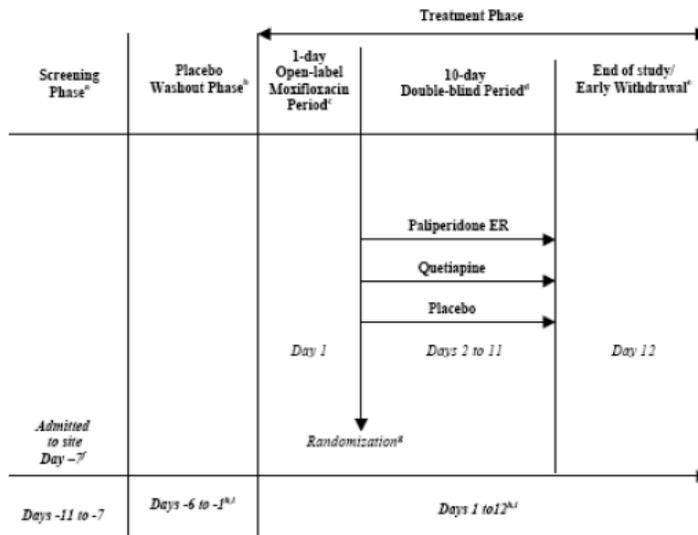
Study Day	-11 to -7	-2 to -1	1	2 to 11	12
<b>Intervention</b>	Screening	Baseline	Moxifloxacin	Multiple dosing	No treatment (Washout)
<b>12-Lead ECGs</b>	None recorded	Record ECGs <sup>###</sup>	Record ECGs <sup>***</sup>	Record ECGs <sup>###</sup>	None recorded
<b>PK Samples for drug</b>	None collected	None collected	None collected	Collected <sup>###</sup>	None collected

<sup>###</sup>0, 1, 2, 3, 4, 4.5, 5, 6, 8, 9, 12, 24 hours postdose

<sup>\*\*\*</sup>0, 1, 1.5, 2.5, and 3.5 hours postdose for moxifloxacin

The quetiapine concentration-time profile and placebo-adjusted, baseline-corrected QTcF profile were shown in Figure 3. The relationship between quetiapine concentrations and QT interval was investigated by using log-linear mixed-effects models. Data collected from the 400 mg bid Quetiapine dose group at day 6 and 11 was used for the Quetiapine concentration-QTcF analysis.

**Figure 2 Schematic Illustration of the Study Design**



<sup>a</sup> Screening lasts up to 5 days.

<sup>b</sup> Subjects will receive placebo for 6 days.

<sup>c</sup> Subjects will receive a single dose of open-label 400-mg moxifloxacin in the morning for 1 day.

<sup>d</sup> Subjects will receive paliperidone ER, quetiapine, or placebo for 10 days. Paliperidone ER was administered beginning with a 12 mg dose on Days 2 to 6, 15 mg dose on Day 7, and an 18 mg dose on Days 8 to 11. Quetiapine was administered beginning with 100 mg twice daily (bid) on Day 2, 200 mg bid on Day 3, 300 mg bid on Day 4, and 400 mg bid on Days 5 to 11, as described in [Section 3.6](#).

<sup>e</sup> End of study evaluations will be performed on subjects at the final visit on Day 12 and on those subjects who withdraw early from the study.

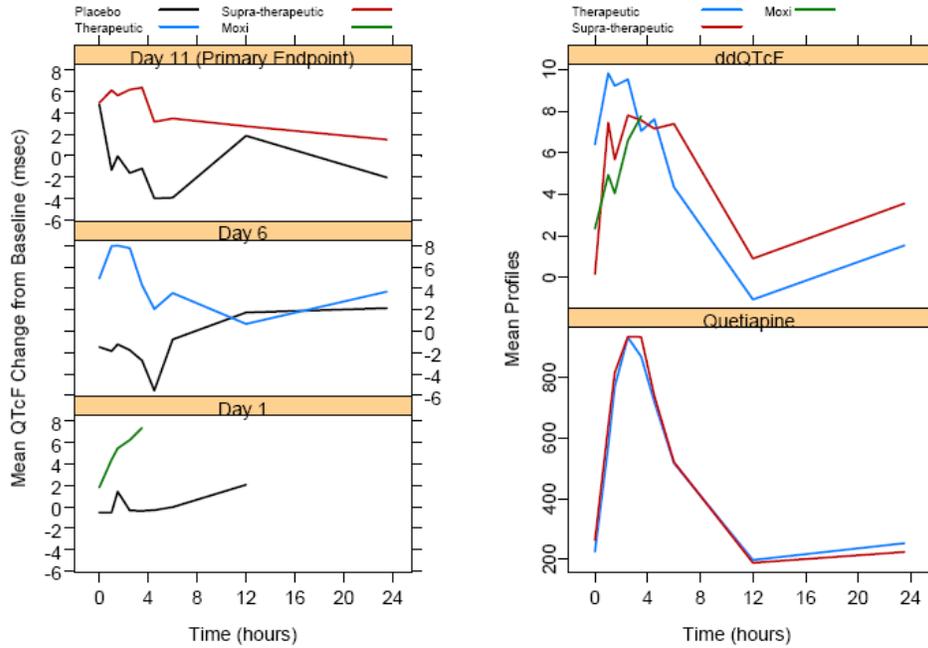
<sup>f</sup> Subjects will be admitted to the site on Day -7 and will remain until study completion on Day 12, or until early withdrawal from the study. Subjects can remain hospitalized longer based on the judgment of the investigator. If more than 3 additional days of hospitalization is required, the additional days must be discussed with the Medical Monitor.

<sup>g</sup> Randomization will occur after study drug administration on Day 1.

<sup>h</sup> Pharmacokinetic blood samples (4 mL each) will be collected on Days -2, -1, 1, 6, 7, 11, and 12 for the determination of plasma concentrations of paliperidone ER and quetiapine. Blood samples will be collected within 5 min after each triplicate ECG recording, where applicable. Refer to the table in [Section 9.1, Study Procedures-Overview](#), for the specific time points of pharmacokinetic blood samples.

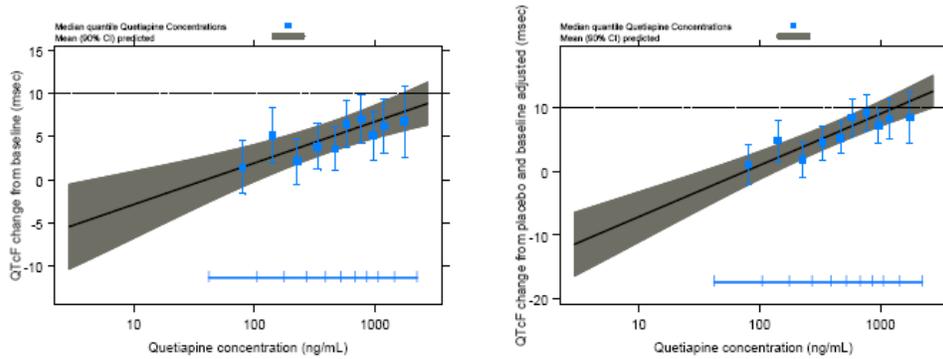
<sup>i</sup> Triplicate 12-lead ECG recordings will be obtained on Days -2, -1, 1, 6, 7, 11 and 12. Refer to the table in [Section 9.1, Study Procedures-Overview](#), for the specific time points of ECG recordings.

**Figure 3 Mean  $\Delta$ QTcF (Change from Baseline) from day 1 to 11 (left),  $\Delta\Delta$ QTcF (top right), and Quetiapine concentration (bottom right) profiles for placebo (black line), 400 mg bid at day 6 (blue line) and day 11 (red line), and moxifloxacin (green line)**



(Source: QT-IRT Review for NDA 21999)

**Figure 4  $\Delta$ QTcF (left) and  $\Delta\Delta$ QTcF (right) vs. quetiapine concentration with observed median-quantile concentrations and associated mean QT (90% CI) prolongation overlaid (blue dots).**



(Source: QT-IRT Review for NDA 21999)

**Table 10 Exposure-Response Analysis of Quetiapine associated  $\Delta$ QTcF and  $\Delta\Delta$ QTcF**

	Estimate (90% CI); p-value	Between-subject variability (SD)
<b>Model 1: <math>\Delta</math>QTcF = Intercept + slope*log(Quetiapine Concentration)</b>		
Intercept, ms	-7.64 (-13.5, -1.80) 0.034	16.3
Slope, ms per log ng/mL	2.08 (1.15, 3.01) 0.0006	2.56
Residual Variability, ms	7.68	--
<b>Model 2: <math>\Delta\Delta</math>QTcF = Intercept + slope*log(Quetiapine Concentration)</b>		
Intercept, ms	-15.2 (-21.2, -9.29) 0.0001	16.7
Slope, ms per log ng/mL	3.52 (2.57, 4.46) <0.0001	2.62
Residual Variability, ms	7.72	--

(Source: QT-IRT Review for NDA 21999)

Based on the concentration-QT relationship, the predicted  $\Delta\Delta$ QTcF values when children and adolescents are administered quetiapine 200 mg, 300 mg, and 400 mg BID are shown in Table 11. Under 200 mg, 300mg, and 400 mg BID dosing, the mean baseline-corrected, placebo-adjusted QTcF values are 5.4, 6.8, and 6.9 ms respectively. The maximal upper bound of 90% confidence interval is less than 9 ms under 400 mg BID dosing.

**Table 11 Model Predicted  $\Delta\Delta$ QTcF Values**

Daily Dose (mg/day)	Dose (mg)	Dosing	C <sub>max</sub> * (ng/mL)	Predicted QTcF (90% CI) (ms)
400	200	BID	520.9	5.4 (3.6 - 7.1)
600	300	BID	1023.6	6.8 (4.9 - 8.7)
800	400	BID	1113.4	6.9 (5.0 - 8.9)

(Note: \* please refer to Dr. Kofi Kumi's review on NDA 20639 for the C<sub>max</sub> values)

## 12 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
QTanalysis.ssc	Analysis Script File	\\cdsnas\PHARMACOMETRICS\Seroquel\Analysis\SPlus

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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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Kofi Kumi  
3/11/2009 07:43:58 PM  
BIOPHARMACEUTICS

Raman Baweja  
3/12/2009 12:39:39 PM  
BIOPHARMACEUTICS

Hao Zhu  
3/12/2009 12:48:59 PM  
BIOPHARMACEUTICS

Christine Garnett  
3/12/2009 01:56:56 PM  
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**020639Orig1s046**

**OTHER 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: 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.

## Medication Guide

SEROQUEL (b) (4) (SER-oh-kwell)  
(quetiapine fumarate)

Tablets (b) (4)

Read this Medication Guide before you start taking SEROQUEL (b) (4) 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. ***[DRISK Comment: For easier readability throughout the Medication Guide (MG), left justify the text, use bulleted statements instead of numbered statements, and do not use italics.] [DRISK Comment: To be consistent throughout the MG (b) (4) was changed to "healthcare provider".]***

**What is the most important information I should know about SEROQUEL (b) (4)**

(b) (4)

(b) (4)

(b) (4)

- 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) 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. *[DRISK Comment: The “What else do I need to know about SEROQUEL was moved to the “What are the side effects of SEROQUEL (b)(4) (b)(4) ” to be consistent with other patient labeling.]*

**What (b)(4) SEROQUEL (b)(4) ?**

- SEROQUEL (b)(4) prescription medicines used to treat (b)(4) (b)(4) Schizophrenia in people age 13 or older. ***[DRISK Comment: the pediatric section 8.4 of Seroquel says that the safety and efficacy of (b)(4) f schizophrenia has not been established. (b)(4) however, this indication is for the long-term treatment of schizophrenia in patients who can be as young as 13. Please clarify this contradiction.]***
- SEROQUEL (b)(4) prescription medicines used to treat (b)(4) (b)(4) bipolar disorder, including:
  - depressive episodes (b)(4)

- manic episodes associated with Bipolar I Disorder alone or with lithium or
- divalproex in adults
- long-term treatment of Bipolar I Disorder with lithium or divalproex in adults

(b) (4)

- SEROQUEL is used to treat manic episodes associated with Bipolar I Disorder in children ages 10 to 17 years.

SEROQUEL (b) (4) patients younger than (b) (4)  
**[DRISK Comment: the pediatric section 8.4 of Seroquel says that it is not approved for patients younger than 18; however, one of the indications is for patients ages 10 to 17, and another indication is for patients ages 13 or older. Please clarify these contradictions.] [DRISK Comment: Medication Guides are to provide information to the patient about the drug product. Disease-specific information such as the symptoms of Bipolar Disorder and Schizophrenia should be moved to the end of the Medication Guide, or preferably addressed to the patient in a separate document.]**

**What should I tell my healthcare provider before taking SEROQUEL** (b) (4)

(b) (4)

Before taking SEROQUEL (b) (4) tell your healthcare provider if you have:

- diabetes or high blood sugar, in you or in your family. Your healthcare provider should check your blood sugar before you start SEROQUEL (b) (4) and also during therapy.
- (b) (4)
- 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 plan to become pregnant. It is not known if SEROQUEL (b) (4) (b) (4) will harm your unborn baby.
- breast-feeding or plan to breast-feed. It is not known if SEROQUEL (b) (4) (b) (4) will pass into your breast milk. You and your healthcare provider should decide if you will take SEROQUEL (b) (4) 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 (b) (4) and other medicines may affect each other causing serious side effects. SEROQUEL (b) (4) may affect the way other medicines work, and other medicines may affect how SEROQUEL (b) (4) works.

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

- depression
- high blood pressure
- Parkinson's disease (b) (4).

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, (b) (4) (an antipsychotic)
- (b) (4)
- ketoconazole, fluconazole or itraconazole (for fungal infections)
- erythromycin (an antibiotic)
- protease inhibitors (for HIV)

***[DRISK Comment: We recommend that this section not include a long list of drugs with single brand names. If the brand name of the patient's medicine is not included, they may think that their medicine is not a problem.]***

This is not a complete list of medicines that can affect (b) (4). Your doctor can tell you if it is safe to take SEROQUEL (b) (4) with your other medicines. Do not start or stop any medicines while taking SEROQUEL (b) (4) 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 (b) (4)?**

- Take SEROQUEL (b) (4) exactly as your healthcare provider tells you to take it. Do not change the dose yourself.
- Take SEROQUEL (b) (4) by mouth, with or without food.
- (b) (4)
- (b) (4)
- If you feel you need to stop SEROQUEL (b) (4) talk with your healthcare provider first.

If you suddenly stop taking SEROQUEL (b) (4), you may experience side effects such as trouble sleeping or 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 (b) (4) call your healthcare provider or poison control center at 1-800- (b) (4) way or go to the nearest hospital emergency room. **[DRISK Comment: The number (1-800-222-1212) must appear with the words: "call your poison control center at 1-800-222-1212".]**

### What should I avoid while taking SEROQUEL (b) (4)?

Do not drive, operate machinery, or do other dangerous activities until you know how SEROQUEL (b) (4) affect you. SEROQUEL and 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 (b) (4), 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 (b) (4). It may make some side effects of SEROQUEL or SEROQUEL XR worse.

### What are the possible side effects of SEROQUEL (b) (4)?

SEROQUEL (b) (4) can cause serious side effects including:

(b) (4) **"What is the most important information I should know about SEROQUEL (b) (4)?"**.

- **High blood sugar (hyperglycemia):** Increase of blood sugar can happen in some people who take SEROQUEL (b) (4). 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 (b) (4) (b) (4) and during therapy.

Call your healthcare provider if you have any of these symptoms of high blood sugar while taking SEROQUEL or 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)**
- **Increase in weight (weight gain)**
- **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 (b) (4) and call your healthcare provider right away.

- **Tardive dyskinesia:** Tell your healthcare provider about any movements (b) (4) that you cannot control. These may be signs of a serious condition. Tardive dyskinesia may not go away, even if you stop taking SEROQUEL (b) (4). Tardive dyskinesia may also start after you stop taking SEROQUEL (b) (4).
- **Orthostatic hypotension:** lightheadedness or fainting caused by a sudden change in heart rate and blood pressure when rising too quickly from a sitting or lying position.
- **Low white blood cell count**
- **Cataracts**
- **Seizures**
- **Abnormal thyroid tests.** Your healthcare provider will do blood tests to check your thyroid hormone level.
- **Increases in prolactin levels.** Your healthcare provider will do blood test to check your prolactin levels.
- **Increases in blood pressure** (b) (4) in children and teenagers
- **Increases in liver enzymes.** (b) (4) healthcare provider will do blood test to check your liver enzyme levels.
- **Long lasting and painful erection**
- **Difficulty swallowing**

**Common possible side effects with SEROQUEL (b) (4) include:**

- drowsiness
- dry mouth
- dizziness
- weakness
- abdominal pain
- constipation
- sore throat
- sluggishness
- stuffy nose
- upset stomach

These are not all the possible side effects of SEROQUEL (b) (4). 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 (b) (4)?**

- Store SEROQUEL (b) (4) at room temperature, between 59°F to 86°F (15°C to 30°C).
- Keep SEROQUEL (b) (4) and all medicines out of the reach of children.

**General information about SEROQUEL (b) (4)**

(b) (4)  
Do not take SEROQUEL (b) (4). Do not share SEROQUEL (b) (4) 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 (b) (4). For more information about SEROQUEL (b) (4) talk with your healthcare provider or pharmacist or call 1-800-236-9933. You can ask your healthcare provider for information about SEROQUEL (b) (4) that is written for health professionals.

**What are the ingredients in SEROQUEL (b) (4) ?**

**Active ingredient:** quetiapine fumarate

**Inactive ingredients:**

(b) (4) povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol, and titanium dioxide. The 25 mg tablets contain red and yellow ferric oxide. The 100 mg and 400 mg tablets contain only yellow ferric oxide

(b) (4)

**The symptoms of Bipolar Disorder:**

- 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 more than normal guilt, changes in sleep or appetite and
- Thoughts of death or suicide.

**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 of everyone (paranoia).

(b) (4)

(b) (4)

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

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Distributed by:

AstraZeneca Pharmaceuticals LP

Wilmington, DE 19850

Made in United Kingdom

SIC XXXX-XX

Medication Guide

(b) (4) SEROQUEL XR (SER-oh-kwell)

(quetiapine fumarate)

(b) (4) Extended-Release Tablets

Read this Medication Guide before you start taking (b) (4) 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. ***[DRISK Comment: For easier readability throughout the Medication Guide (MG), left justify the text, use bulleted statements instead of numbered statements, and do not use italics.] [DRISK Comment: To be consistent throughout the MG (b) (4) was changed to "healthcare provider".]***

**What is the most important information I should know about (b) (4) SEROQUEL XR?**

- [Redacted] (b) (4)

- [Redacted] (b) (4)

**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) 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. *[DRISK Comment: The "What else do I need to know about (b) (4) was moved to the "What are the side effects of (b) (4) SEROQUEL XR?" to be consistent with other patient labeling.]*

**What (b) (4) SEROQUEL XR?**

- (b) (4) SEROQUEL XR (b) (4) prescription medicines used to treat (b) (4) Schizophrenia in people age 13 or older. *[DRISK Comment: the pediatric section 8.4 of Seroquel says that the safety and efficacy of (b) (4) of schizophrenia has not been established, (b) (4) this indication is for the long-term treatment of schizophrenia in patients who can be as young as 13. Please clarify this contradiction]*
- (b) (4) SEROQUEL XR (b) (4) prescription medicines used to treat (b) (4) bipolar disorder, including:
  - depressive episodes (b) (4)
  - manic episodes associated with Bipolar I Disorder alone or with lithium or divalproex in adults
  - long-term treatment of Bipolar I Disorder with lithium or divalproex in adults

(b) (4)

(b) (4)

(b) (4) SEROQUEL XR (b) (4) not approved for patients (b) (4) 18 years. *[DRISK Comment: the pediatric section 8.4 of Seroquel says that it is not approved for patients younger than 18; however, one of the indications is for patients ages 10 to 17, and another indication is for patients ages 13 or older. Please clarify these contradictions.] [DRISK Comment: Medication Guides are to provide information to the patient about the drug product. Disease-specific information such as the symptoms of Bipolar Disorder and*

**Schizophrenia should be moved to the end of the Medication Guide, or preferably addressed to the patient in a separate document.**

**What should I tell my healthcare provider before taking [REDACTED] (b) (4) SEROQUEL XR?**

Before taking [REDACTED] (b) (4) SEROQUEL XR, tell your healthcare provider if you have:

- diabetes or high blood sugar, in you or in your family. Your healthcare provider should check your blood sugar before you start [REDACTED] (b) (4) SEROQUEL XR and also during therapy.
- [REDACTED] (b) (4)
- 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 plan to become pregnant. It is not known if [REDACTED] (b) (4) SEROQUEL XR will harm your unborn baby.
- breast-feeding or plan to breast-feed. It is not known if [REDACTED] (b) (4) SEROQUEL XR will pass into your breast milk. You and your healthcare provider should decide if you will take [REDACTED] (b) (4) 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.

[REDACTED] (b) (4) SEROQUEL XR and other medicines may affect each other causing serious side effects. [REDACTED] (b) (4) SEROQUEL XR may affect the way other medicines work, and other medicines may affect how [REDACTED] (b) (4) SEROQUEL XR works.

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

- depression
- high blood pressure
- Parkinson's disease [REDACTED] (b) (4).

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, [REDACTED] (b) (4) (an antipsychotic)
- [REDACTED] (b) (4)
- ketoconazole, fluconazole or itraconazole (for fungal infections)
- erythromycin (an antibiotic)
- protease inhibitors (for HIV)

***[DRISK Comment: We recommend that this section not include a long list of drugs with single brand names. If the brand name of the patient's medicine is not included, they may think that their medicine is not a problem.]***

This is not a complete list of medicines that can affect (b) (4) SEROQUEL XR. Your doctor can tell you if it is safe to take (b) (4) SEROQUEL XR with your other medicines. Do not start or stop any medicines while taking (b) (4) 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 (b) (4) SEROQUEL XR?**

- Take (b) (4) SEROQUEL XR exactly as your healthcare provider tells you to take it. Do not change the dose yourself.
- Take (b) (4) SEROQUEL XR by mouth, with or without food.
- (b) (4)
- (b) (4) SEROQUEL XR should be swallowed whole and not split, chewed or crushed.
- If you feel you need to stop (b) (4) SEROQUEL XR, talk with your healthcare provider first.

If you suddenly stop taking (b) (4) SEROQUEL XR, you may experience side effects such as trouble sleeping or 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 (b) (4) 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. ***[DRISK Comment: The number (1-800-222-1212) must appear with the words: "call your poison control center at 1-800-222-1212".]***

### **What should I avoid while taking (b) (4) SEROQUEL XR?**

Do not drive, operate machinery, or do other dangerous activities until you know how (b) (4) SEROQUEL XR affect you. (b) (4) 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 (b) (4) 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 (b) (4) SEROQUEL XR. It may make some side effects of (b) (4) SEROQUEL XR worse.

## What are the possible side effects of (b) (4) SEROQUEL XR?

(b) (4) SEROQUEL XR can cause serious side effects including:

See “What is the most important information I should know about (b) (4) SEROQUEL XR?”.

- **High blood sugar (hyperglycemia):** Increase of blood sugar can happen in some people who take (b) (4) 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 (b) (4) SEROQUEL XR and during therapy.

Call your healthcare provider if you have any of these symptoms of high blood sugar while taking SEROQUEL or 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)**
- **Increase in weight (weight gain)**
- **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 (b) (4) SEROQUEL XR and call your healthcare provider right away.
- **Tardive dyskinesia:** Tell your healthcare provider about any movements (b) (4) that you cannot control. These may be signs of a serious condition. Tardive dyskinesia may not go away, even if you stop taking (b) (4) SEROQUEL XR. (b) (4) may also start after you stop taking (b) (4) SEROQUEL XR.
- **Orthostatic hypotension:** lightheadedness or fainting caused by a sudden change in heart rate and blood pressure when rising too quickly from a sitting or lying position.
- **Low white blood cell count**
- **Cataracts**
- **Seizures**
- **Abnormal thyroid tests.** Your healthcare provider will do blood tests to check your thyroid hormone level.
- **Increases in prolactin levels.** Your healthcare provider will do blood test to check your prolactin levels.

- **Increases in blood pressure** (b) (4) in children and teenagers
- **Increases in liver enzymes.** Your healthcare provider will do blood test to check your liver enzyme levels.
- **Long lasting and painful erection**
- **Difficulty swallowing**

**Common possible side effects with (b) (4) SEROQUEL XR include:**

- |                  |                 |
|------------------|-----------------|
| • drowsiness     | • constipation  |
| • dry mouth      | • sore throat   |
| • dizziness      | • sluggishness  |
| • weakness       | • stuffy nose   |
| • abdominal pain | • upset stomach |

These are not all the possible side effects of (b) (4) 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 (b) (4) SEROQUEL XR?**

- Store (b) (4) SEROQUEL XR at room temperature, between 59°F to 86°F (15°C to 30°C).
- Keep (b) (4) SEROQUEL XR and all medicines out of the reach of children.

**General information about (b) (4) SEROQUEL XR.**

(b) (4)  
 . Do not take (b) (4) SEROQUEL XR (b) (4)  
 Do not share (b) (4) 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 (b) (4) (b) (4) SEROQUEL XR. For more information about (b) (4) SEROQUEL XR talk with your healthcare provider or pharmacist or call 1-800-236-9933. You can ask your healthcare provider for information about (b) (4) SEROQUEL XR that is written for health professionals.

**What are the ingredients in (b) (4) SEROQUEL XR?**

**Active ingredient:** quetiapine fumarate

(b) (4)

**SEROQUEL XR:** lactose monohydrate, microcrystalline cellulose, sodium citrate, hypromellose, magnesium stearate, polyethylene glycol 400 and titanium dioxide. (b) (4)  
50mg, 200mg and 300mg tablets (b) (4) yellow iron oxide and the 50mg tablets (b) (4)  
(b) (4) red iron oxide

**The symptoms of Bipolar Disorder:**

- 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 (b) (4) guilt, changes in sleep or appetite and
- Thoughts of death or suicide.

**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 (b) (4) (paranoia).

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

- 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 (b) (4) guilt
- Changes in sleep or eating patterns
- Thoughts of death or suicide.

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

(b) (4) SEROQUEL XR (b) (4) trademarks of the AstraZeneca group of companies.

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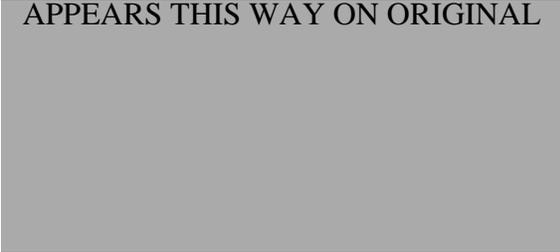
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LATONIA M FORD  
08/28/2009

JODI M DUCKHORN  
08/28/2009



**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: April 17, 2009

To: Mark Ritter, Medical Officer  
Division of Psychiatry Products  
Office of New Drugs

Through: Laura Governale, PharmD, MBA  
Drug Use Data Analyst Team Leader  
Division of Epidemiology  
Office of Surveillance and Epidemiology

From: Hina Mehta, PharmD  
Drug Use Data Analyst  
Division of Epidemiology  
Office of Surveillance and Epidemiology

Subject: Total number of prescriptions and patients for Seroquel<sup>®</sup>  
(quetiapine), Zyprexa<sup>®</sup> (olanzapine), and Geodon<sup>®</sup> (ziprasidone)

Drug Name(s): Seroquel<sup>®</sup> (quetiapine), Zyprexa<sup>®</sup> (olanzapine), and Geodon<sup>®</sup>  
(ziprasidone)

Application Type/Number: Various

Applicant/sponsor: Various

OSE RCM #: 2009-439

## 1 INTRODUCTION

The Division of Psychiatry Products (DPP) is preparing for a presentation at the PDAC meeting. The committee will be asked to vote on whether or not Seroquel<sup>®</sup> (quetiapine), Zyprexa<sup>®</sup> (olanzapine), and Geodon<sup>®</sup> (ziprasidone) have been shown to be effective and acceptably safe for pediatric indications. In support of that presentation, the Division of Epidemiology (DEPI) has been requested to provide prescription and patient utilization data in the pediatric population for Seroquel<sup>®</sup> (quetiapine), Zyprexa<sup>®</sup> (olanzapine), and Geodon<sup>®</sup> (ziprasidone), for years 2004 through 2008.

## 2 METHODS AND MATERIAL

### 2.1 DETERMINING SETTINGS OF CARE AND DATA SOURCES USED

The IMS Health, IMS National Sales Perspectives<sup>™</sup> (see Appendix 1 for database descriptions) was used to determine the various retail and non-retail channels of distribution for Seroquel<sup>®</sup> (quetiapine), Zyprexa<sup>®</sup> (olanzapine), and Geodon<sup>®</sup> (ziprasidone).<sup>1</sup> The examination of wholesale sales data by eaches (packets, bottles, etc.) in year 2008 indicate that the majority of distribution for most of these products is toward outpatient pharmacy settings <sup>(b) (4)</sup> or greater). Outpatient pharmacy settings include chain, independent, and food stores with pharmacies. Distribution towards non-retail pharmacy settings ranged from <sup>(b) (4)</sup> to <sup>(b) (4)</sup> during year 2008. The long term care setting within the non-retail channels received the majority of quetiapine and olanzapine sales. Mail order distribution ranged from <sup>(b) (4)</sup> to <sup>(b) (4)</sup> for the three agents analyzed. Thus, we examined outpatient utilization patterns. Mail order and long term care data are not included in this analysis.

### 2.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

We examined total dispensed prescriptions by product using SDI, Vector One<sup>®</sup>: National (VONA) (see Appendix 1 for full description) for calendar years 2004 through 2008. We also examined the number of patients who received a prescription for quetiapine, olanzapine, or ziprasidone products using SDI, Vector One<sup>®</sup>: Total Patient Tracker (TPT) for calendar years 2004 through 2008. Diagnosis associated with the use of these products, as reported by office-based physicians, were determined using SDI's Physician Drug and Diagnosis Audit (PDDA) for calendar years 2002 through 2008.

## 3 DATA

### 3.1 OUTPATIENT DISPENSED PRESCRIPTIONS

Table 1 in Appendix 2 shows the total number of prescriptions dispensed in the outpatient retail setting (mail order excluded) for Seroquel<sup>®</sup> (quetiapine), Zyprexa<sup>®</sup> (olanzapine), and Geodon<sup>®</sup> (ziprasidone). During year 2008, approximately <sup>(b) (4)</sup> million prescriptions were dispensed for quetiapine followed by olanzapine and ziprasidone with <sup>(b) (4)</sup> million and <sup>(b) (4)</sup> million prescriptions, respectively. Both quetiapine and ziprasidone products realized an increase in the number of

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<sup>1</sup> IMS Health, IMS Nationals Sales Perspectives<sup>™</sup>, Years 2004-2008. Data extracted 4-1-09. File: 0904psyc.dvr

dispensed prescriptions in the past 5 years except for olanzapine which decreased by about a third during the time period. Prescriptions dispensed to pediatric patients aged 0-12 years accounted for less than (b) (4) of the total dispensed prescriptions for all three agents. Adolescents aged 13-17 years accounted for approximately (b) (4) of dispensed prescriptions of ziprasidone followed by (b) (4) and (b) (4) of quetiapine and olanzapine, respectively.

### 3.2 PATIENT COUNT

Trends for patient data were similar to that of prescription data (Appendix 2: Table 2). During year 2008, approximately (b) (4) million patients received a prescription for quetiapine while (b) (4) patients received a prescription for olanzapine and (b) (4) received ziprasidone. Pediatric patients aged 0-12 years accounted for less than (b) (4) of patients receiving a prescription for each of the agents studied. Adolescents aged 13-17 years accounted for approximately (b) (4) of patients receiving a prescription for ziprasidone followed quetiapine and olanzapine with (b) (4) and (b) (4), respectively.

### 3.3 DIAGNOSIS ASSOCIATED WITH USE

We also examined the most common diagnosis associated with the use of Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) as reported by office-based physician practices in the U.S. (Appendix 2: Tables 3a, 3b, and 3c). “Affective Psychoses” ICD-9 296 was the most common diagnosis associated with the use of quetiapine with approximately 46% of all uses in year 2008 followed by “Schizophrenic Disorders” ICD-9 295 with 21%. For olanzapine and ziprasidone the most common diagnosis was “Schizophrenic Disorders” ICD-9 295 with 42% and 40%, respectively, followed by “Affective Psychoses” with 33% and 35%, respectively.

### 3.4 PRESCRIBER SPECIALTY

Table 4 in Appendix 2 shows the total number of prescriptions dispensed for Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) by physician specialty. The majority of prescriptions dispensed for all three were prescribed by Psychiatrists (b) (4)% for quetiapine, (b) (4)% for olanzapine, and (b) (4)% for ziprasidone) over the entire study period. Unspecified physicians prescribed approximately (b) (4)% of prescriptions dispensed for all three agents during year 2008. Approximately (b) (4)% of prescriptions dispensed were prescribed by General Practice/Family Medicine/Doctor of Osteopathy for both quetiapine and olanzapine and (b) (4)% for ziprasidone during year 2008.

## 4 DISCUSSION

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) are distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these outpatient retail pharmacy channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Indications for use were obtained using SDI’s PDDA, a monthly survey of 3,200 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for

the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time.

## 5 CONCLUSIONS

The majority of sales of Seroquel<sup>®</sup> (quetiapine), Zyprexa<sup>®</sup> (olanzapine), and Geodon<sup>®</sup> (ziprasidone) were to outpatient retail pharmacy settings. During year 2008, approximately (b) (4) million prescriptions were dispensed for quetiapine followed by olanzapine and ziprasidone with (b) (4) million and (b) (4) million prescriptions, respectively. Prescriptions dispensed to pediatric patients aged 0-12 years accounted for less than (b) (4)% of the total dispensed prescriptions for all three agents. Adolescents aged 13-17 years accounted for approximately (b) (4)% of dispensed prescriptions of ziprasidone followed by (b) (4)% and (b) (4)% of quetiapine and olanzapine, respectively. The trends for patient data were similar to prescription data. The most common diagnosis associated with the use of the three agents is “Affective Psychoses” ICD-9 296 and “Schizophrenic Disorders” ICD-9 295. Psychiatrists were the most common prescribers for all three of the agents studied.

## **APPENDIX 1: DATABASE DESCRIPTIONS**

### ***SDI Vector One®: National (VONA)***

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

### ***SDI Vector One®: Total Patient Tracker (TPT)***

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

### ***IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail***

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

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DRUG SAFETY OFFICE REVIEWER

Laura Governale  
5/11/2009 11:09:00 AM  
DRUG SAFETY OFFICE REVIEWER

**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:** April 27, 2009

**TO:** Kimberly Updegraff, Regulatory Project Manager  
Ni Khin, 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 20-639 SE 45/46

**APPLICANT:** Astra Zeneca Pharmaceuticals LP

**DRUG:** Quetiapine Fumarate Tablets (Seroquel)

**NME:** Not a new molecular entity (NME)

**INDICATIONS:** Treatment of schizophrenia in adolescents (age 13 - 17)  
Treatment of bipolar disorder in children (age 10 - 12) and adolescents

**THERAPEUTIC CLASSIFICATION:** Priority

**CONSULTATION REQUEST DATE:** December 8, 2008

**DIVISION ACTION GOAL DATE:** March 28, 2009

**PDUFA DATE:** April 28, 2009

## **I. BACKGROUND**

Seroquel is an atypical antipsychotic agent previously approved in the US for the treatment of schizophrenia and bipolar disorder, as follows: (1) bipolar depression in adults, (2) bipolar mania in adults, children, and adolescents, (3) bipolar maintenance in adults, and (4) schizophrenia in adults and adolescents. Recently, the use of antipsychotic agents in children has been increasing, as has been the negative publicity regarding their use in children. Under this NDA supplement, the sponsor (AstraZeneca Pharmaceuticals LP) seeks to expand the labeled use of Seroquel to treat schizophrenia and bipolar mania in children (pediatric exclusivity determination). The sponsor presents clinical data from two major pivotal studies.

### Pivotal Clinical Studies

Study D1441C00112 was a pivotal, 6-week, randomized, double-blind, placebo-controlled study of Seroquel in daily doses of 400 mg and 800 mg in the treatment of adolescents with schizophrenia. The study was conducted at 43 centers internationally, from October 2004 through June 2007. The primary objective of the study was to compare the efficacy of the two dose levels of Seroquel with that of placebo, as assessed by the change from baseline to Day 42 in the Positive and Negative Syndrome Scale (PANSS) total score. Patients were randomly assigned to blinded study treatment in a 1:1:1 ratio. Double-blind treatment was preceded by a medication washout period of 1 to 28 days. The patients were treated as either inpatient or outpatient throughout the course of the study, according to the clinical judgment of the clinical investigator.

Study D1441C00149 was a pivotal, 3-week, randomized, double-blind, placebo-controlled study of Seroquel in daily doses of 400 mg and 600 mg in the treatment of adolescents with bipolar mania. The study was conducted at 34 centers in the United States, from August 2004 through July 2006. The primary objective of the study was to compare the efficacy of the two dose levels of Seroquel with that of placebo, as assessed by the change from baseline to Day 21 in the Young Mania Rating Scale (YMRS) total score. Patients were randomly assigned to blinded study treatment in a 1:1:1 ratio and stratified by age group (10 to 12 years and 13 to 17 years). Double-blind treatment was preceded by a medication washout period of 1 to 28 days. The patients were treated as either inpatient or outpatient throughout the course of the study, according to the clinical judgment of the clinical investigator.

## **II. SELECTION OF CLINICAL SITES FOR INSPECTION**

For each of the two pivotal studies, Division of Psychiatry Products (DPP) selected three clinical sites that appeared to be important contributors to the overall efficacy results (two US sites, one foreign site in Russia). For Study D1441C00112, the site in Russia appeared to be particularly important; removing the data from this site yields negative efficacy results for the low dose group and marginally positive results for the high-dose group. Division of Scientific Investigations (DSI) performed a site-specific efficacy analysis in support of site selection, as further discussed below.

For each of the two pivotal studies, Tables 1 and 2 below present efficacy results from sites that enrolled at least two subjects into both the placebo and Seroquel groups. For each clinical site, an efficacy index (EI) was calculated as a measure of the site's contribution to the overall study, relative to the contribution from all other sites in either study. EI values are shown in the last column of each Table.

**Table 1: Study D1441C00112 (Primary Efficacy Endpoint = PANSS)**

Site	Seroquel		Placebo		Seroquel - Placebo		Efficacy Index
	N	Mean Change PANSS	N	Mean Change PANSS	Difference	Site-Specific Efficacy (SSE)	
240	6	-24.2	4	4.5	-28.7	3.46	20.8
342	10	-38.5	4	-22.5	-16	1.93	19.3
24	4	-25.8	3	9.1	-34.8	4.2	16.8
280	10	-14.8	5	-2	-12.8	1.55	15.5
321	4	-18.5	2	9.5	-28	3.38	13.5
41	6	-24.7	3	-11	-13.7	1.65	9.9
261	4	-28.8	2	-11	-17.8	2.14	8.6
3	2	-35.5	2	-3	-32.5	3.92	7.8
282	4	-14.8	3	0	-14.8	1.78	7.1
10	4	-21.8	2	-8	-13.8	1.66	6.6
54	3	-35.7	2	-19.5	-16.2	1.95	5.9
263	4	1	2	12.5	-11.5	1.39	5.6
241	8	-14.9	3	-11	-3.9	0.47	3.8
242	11	-11	5	-9	-2	0.24	2.6
220	3	-28.3	2	-25.5	-2.8	0.34	1.0
26	2	-48.5	2	-46	-2.5	0.3	0.6
260	2	-11	3	-13	2	-0.24	-0.5
362	4	-25	2	-30	5	-0.6	-2.4
49	4	-62	2	-73	11	-1.33	-5.3
341	7	-29	2	-37.5	8.5	-1.03	-7.2
262	6	-48.7	3	-68.7	20	-2.41	-14.5

**Table 2: Study D1441C00149 (Primary Efficacy Endpoint = YMRS)**

Site	Seroquel		Placebo		Seroquel - Placebo		Efficacy Index
	N	Mean Change YMRS	N	Mean Change YMRS	Difference	Site-Specific Efficacy (SSE)	
19	16	-18.3	8	-0.5	-17.8	3.2	51.2
38	11	-12.4	6	-4.8	-7.5	1.35	14.9
40	10	-14.8	4	-7.5	-7.3	1.31	13.1
26	8	-14.6	3	-5.7	-9	1.61	12.9
28	5	-20.2	2	-8	-12.2	2.19	11.0
10	18	-17.7	8	-14.4	-3.3	0.6	10.8
31	12	-13.5	7	-8.7	-4.8	0.86	10.3
20	8	-14.4	4	-8	-6.4	1.14	9.1
34	6	-11.8	2	-3.5	-8.3	1.5	9.0
41	4	-14.8	3	-5	-9.8	1.75	7.0
24	7	-14.6	4	-10.8	-3.8	0.69	4.8
35	8	-8.6	4	-5.8	-2.9	0.52	4.2
3	6	-19.2	3	-17	-2.2	0.39	2.3
8	6	-5.7	5	-4.2	-1.5	0.26	1.6
4	8	-9	3	-8.3	-0.7	0.12	1.0
2	10	-16.3	4	-17.3	0.9	-0.17	-1.7
17	7	-7	2	-9.5	2.5	-0.45	-3.2
13	8	-5.9	5	-9.8	3.9	-0.7	-5.6
47	7	-16	3	-20.7	4.7	-0.84	-5.9

- In Study D1441C00112, the primary efficacy endpoint was the change from baseline to Day 42 in the Positive and Negative Syndrome Scale (PANSS) score. Site-specific efficacy (SSE) was calculated as:  $SSE = (\text{SEROQUEL mean change in PANSS} - \text{PLACEBO mean change in PANSS}) / -8.3$ , where the value -8.3 serves as a measure of SEROQUEL efficacy for the entire study, using PANSS as the primary efficacy endpoint (SEROQUEL mean change in PANSS - PLACEBO mean change in PANSS = -8.3).
- In Study D1441C00149, the primary efficacy endpoint was the change from baseline to Day 21 in the Young Mania Rating Scale (YMRS) score. Site-specific efficacy (SSE) was calculated as:  $SSE = (\text{SEROQUEL mean change in YMRS} - \text{PLACEBO mean change in YMRS}) / -5.6$ , where the value -5.6 serves as a measure of SEROQUEL efficacy for the entire study, using YMRS as the primary efficacy endpoint (SEROQUEL mean change in YMRS - PLACEBO mean change in YMRS = -5.6).
- Using the SSE value and the number of subjects enrolled (N) at a given site, an efficacy index (EI) for that site was calculated as a quantitative measure of that site's contribution to the overall study result for efficacy, relative to the contribution from all other sites in either study:  $EI = ER \times N$ .

For each study, the clinical sites were ranked in order of descending EI values, as shown in the two tables above. The three sites identified by the review division are shown highlighted. Site 240 (Kozlova, Russia) has the highest EI value for Study D1441C00112, and Site 19 (Rease, California) has the highest EI value for Study D1441C00149. Site 24 (Wamboldt, Colorado) has relatively high EI values in both studies.

### III. INSPECTION RESULTS

The results of the good clinical practice (GCP) inspections for the 3 sites are summarized in Table 3, which uses the following column headings and abbreviations:

- 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)
- Field Classification: field investigator's initial recommendation in classifying the inspection result, pending = final EIR from the field investigator not received at DSI
- Final Classification: CDER's final classification at post-inspectional correspondence (letter to the clinical investigator), pending = DSI review of final EIR and/or issuance of post-inspectional correspondence not completed

**Table 3: Inspection Summary**

	Clinical Study Site	Site Protocol Subjects	Inspection Dates	Classification	
				Field	Final
1	Marianne Wamboldt, MD The Children's Hospital 1056 East 19th Avenue, Box 115 Denver, CO 80218	Site 024 D1441C00112 7 subjects	March 4 - 19 2009	VAI	VAI
		Site 024 D1441C00149 11 subjects			
2	Joachim Rease, MD Behavioral Health 2000, LLC 5945 Brockton Avenue Riverside, CA 92506	Site 019 D1441C00149 26 subjects	March 9 - 13 2009	NAI	NAI
3	Irina A. Kozlova, MD, PhD Mental Health Research Center Russian Academy of Medical Sciences Kashirskoye shosse, 34 Moscow 115522, Russia	Site 240 D1441C00112 10 subjects	March 10 - 13 2009	NAI	NAI

**1. Marianne Wamboldt, MD (Site 24):**

The Children's Hospital  
1056 East 19th Avenue, Box 115  
Denver, CO 80218

**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:
  - Study D1441C00112: 8 subjects were screened, 7 enrolled, and 4 completed the study. Complete records were reviewed for the 4 subjects completing the study.
  - Study D1441C00149: 15 subjects were screened, 11 enrolled, and 10 completed the study. Complete records were reviewed for the 10 subjects completing the study.

- b. General observations and commentary: IRB oversight and study monitoring were adequate. A Form FDA 483 was issued for the following deficiencies:
  - In Study D1441C00149, the conduct of the interview for K-SADS-PL was not always documented (at least 4 subjects)
  - In both studies, the investigational drug disposition records were incomplete (one subject) or internally inconsistent with respect to dates of drug receipt and quantity of drug received (5 subjects, study coordinator versus pharmacy records)
- c. Assessment of data integrity: The observed deficiencies do not appear to have had a significant impact on the study data. Data from this study site (Site 24, Studies D1441C00112 and D1441C00149) appear reliable.

**2. Joachim Rease, MD (Site 19):**

Behavioral Health 2000, LLC  
5945 Brockton Avenue  
Riverside, CA 92506

- 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: 33 subjects were screened, 26 enrolled in study D1441C00149, and 12 completed the study. Complete records were reviewed for 9 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 19, Study D1441C00149) appear reliable.

**3. Irina A. Kozlova, MD, PhD (Site 240):**

Mental Health Research Center  
Russian Academy of Medical Sciences  
Kashirskoye shosse, 34  
Moscow 115522, Russia

- 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: 10 subjects were screened and enrolled in study D1441C00112. Six subjects completed the study. Complete records were reviewed for all 10 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 240, Study D1441C00112) appear reliable.

#### **IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

No significant deficiencies were observed at the three clinical sites selected for inspection in support of this NDA. A Form FDA 483 was issued at Site 24 (Wamboldt) for deficiencies that do 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.

{See appended electronic signature page}

John Lee, MD  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, MD  
Branch Chief, Good Clinical Practice Branch II  
Division of Scientific Investigations  
Office of Compliance

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Tejashri Purohit-Sheth  
4/27/2009 03:52:01 PM  
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**020639Orig1s046**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**



Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

Office of Compliance

REMS Assessment Memorandum

TO: NDA 20639

THROUGH: Tamika White, Acting Branch Chief  
Postmarket Safety Branch  
Division of Safety Compliance  
Office of Scientific Investigations

FROM: Kendra Biddick, CSO  
REMS Compliance Team  
Postmarket Safety Branch  
Division of Safety Compliance  
Office of Scientific Investigations

SUBJECT: 18-month REMS assessment report for Seroquel (quetiapine fumarate)  
Tablets, from AstraZeneca

### **Review Summary**

The assessment was received May 31, 2011, on time, and appears to be complete. If FDA decides to retain this REMS in force, the timetable for submission of assessments should be updated to include the month, day, and year of the original approval of the REMS.

### **Background**

The Medication Guide only REMS for Seroquel was approved December 2, 2009. The goal of the REMS is to inform patients about the serious risks associated with the use of SEROQUEL® (quetiapine fumarate) Tablets. The REMS Elements include:

1. Medication Guide
2. Timetable for Submission of Assessments  
18-months, 3- and 7-years after FDA approval

There are no post approval studies or clinical trials required under section 505(o) included in the approval letter for Seroquel.

The Assessment Plan for the Seroquel REMS includes the following:

1. An evaluation of patients' understanding of the serious risks of Seroquel.

2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

## **OC Observations**

This REMS assessment was due on June 2, 2011, and received on May 31, 2011, on time.

All required elements of the assessment plan were addressed in the assessment. OC defers analysis of the evaluation of patients understanding of the serious risks of Seroquel to OSE.

The patient survey included questions to assess the distribution of the Medication Guide:

The analysis of distribution and dispensing of the medication guide showed that 83 percent (n= 374) of all patients or caregivers reported receiving the Seroquel Medication Guide. Eighteen percent said they received it from the doctor's office. Ninety four percent said they received it from the pharmacy.

AstraZeneca stated that 7.3 percent of survey respondents stated they did not receive a medication guide, and proposes to send another communication to dispensing pharmacies notifying them of the availability of the medication guide and the requirement to provide it with each prescription. OC defers analysis of this proposal to OSE and OND.

The language in the timetable for submission of assessments is the standard language, except that it lacks the month, day, and year of the approval date.

## **OC Recommendations**

If FDA decides to continue this REMS, the first sentence of the timetable for submission of assessments should be amended to include the month, day and year of the original approval date, as follows:

AstraZeneca will submit REMS Assessments to FDA 18 months, 3 years and 7 years from the **initial** date of the approval of the REMS, (**December 2, 2009**).

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/s/  
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KENDRA A BIDDICK  
11/22/2011  
revised

TAMIKA T WHITE  
11/30/2011

## 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/BLA #s:** 20-639 S045/S046  
**Products:** Seroquel Tablets; Quetiapine fumarate (Immediate-Release) Tablets  
**SPONSOR:** AstraZeneca  
**FROM:** Thomas Laughren, MD, Director, Division of Psychiatry Products  
**DATE:** September 21, 2009

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Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS for an approved drug 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)). 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).

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 (quetiapine fumarate) to ensure that the benefits of the drug outweigh the risks of hyperglycemia, hyperlipidemia, and weight gain associated with all forms of Seroquel (quetiapine fumarate). In reaching this determination, we considered the following:

- A. Schizophrenia affects about 1% of the population (DSM-IV-TR, APA 2000). The estimated number of patients in the United States with schizophrenia is about 2.4 million (Regier et. al., 1993).

The estimated prevalence of bipolar disorder is about 0.4 to 1.6% ( DSM-IV-TR, APA 2000). The estimated number of patients in the United States with bipolar disorder is about 5.7 million (Kessler et. al., 2005).

During year 2008, approximately (b) (4) million prescriptions were dispensed for Seroquel (quetiapine fumarate). Prescriptions dispensed to pediatric patients aged 0-

12 years accounted for less than (b) (4) of the total dispensed prescriptions for all three agents. Adolescents aged 13-17 years accounted for approximately (b) (4) of dispensed prescriptions of quetiapine.

- B. Schizophrenia is a serious mental illness that includes disorder of thinking, disorganized behavior, deficits in cognition, affect, and social functioning. It is a chronic and debilitating illness that affects many aspects of a patient's life and has been associated with reduced life expectancy (AACAP 2001, APA 2000a, APA 2004). Adolescents with schizophrenia, like affected adults, have significant impairment, including similar thought disorder, deficits in cognition, affect, and social functioning. Childhood onset schizophrenia is a clinically severe form of schizophrenia in which the disruption in cognitive, linguistic, and social development can occur before the appearance of psychotic symptoms (Jacobsen and Rapoport 1998).

Bipolar disorder is a lifelong psychiatric illness that is characterized by significant morbidity and mortality and is often progressive (Lish et al 1994). Children and adolescents with mania, like affected adults, have significant social impairment leading to conflict within the family, repeated hospitalization, and increased economic burden on the family (Findling et al 2003, Papolos and Papolos 1999). Adolescents with bipolar disorder have an increased risk of substance-abuse disorders (Wilens et al 1999).

- C. Prior to approval of this set of NDA supplements for pediatric schizophrenia and bipolar disorder, there were limited therapeutic options approved for pediatric patients with schizophrenia and bipolar mania. Seroquel (quetiapine fumarate) demonstrated efficacy as compared to placebo in two clinical trials (one in adolescents 13 to 17 years of age and one in children and adolescents 10 to 17 years of age). Seroquel (quetiapine fumarate) has been shown to reduce the psychotic signs and symptoms in adolescent patients with schizophrenia (13 to 17 years of age) and to reduce manic symptoms in pediatric patients with bipolar mania (aged 10 to 17 yrs) when compared to placebo in clinical trials. Seroquel (quetiapine fumarate) is approved in the US for the treatment of adult patients with schizophrenia and mania.
- D. The expected duration of therapy with Seroquel (quetiapine fumarate) in patients who obtain a clinical response will minimally be 6 months to a year, and may be for many years; schizophrenia and bipolar disorder are considered life-long diseases, although the severity of symptoms may vary over time.
- E. Several safety concerns have been identified in the adult clinical trials programs for quetiapine. Known potential safety signals include weight gain, hyperlipidemia, hyperglycemia, and potential clinical worsening of suicidality (class effect associated in certain age groups). Based on the DPP review of safety data included in the pending pediatric efficacy supplements for schizophrenia and bipolar disorder under NDA-20639/S-045 and 046, the submissions revealed consistent findings with the

previously observed safety profile of Seroquel (quetiapine fumarate) immediate and extended release formulations in adult clinical trials.

The current Seroquel (quetiapine fumarate) label contains Warning language describing an association with hyperglycemia, diabetes mellitus, weight gain, and lipid elevations. 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 (quetiapine fumarate).

F. Seroquel (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 (quetiapine fumarate). FDA has determined that Seroquel (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 (quetiapine fumarate). FDA has determined that Seroquel (quetiapine fumarate) 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 (quetiapine fumarate).

The elements of the REMS will be a revised MedGuide 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

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/s/  
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KIMBERLY S UPDEGRAFF  
09/25/2009

THOMAS P LAUGHREN  
09/25/2009

December 8, 2009

This REMS Memo is obsolete and has been replaced by the REMS Memo dated 9-25-09. The 9-25-09 memo has additional comments from SRT & SWAT and should be referred to as the justification for the REMS Notification Letter issued for supplements 045 and 046 by the Division of Psychiatry Products on 9-25-09.

**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**

**NDA/BLA #s:** 20-639 S045/S046 **Products:** Seroquel Tablets; Quetiapine fumarate  
(Immediate-Release)

Tablets **SPONSOR:** AstraZeneca **FROM:** Thomas Laughren, MD, Director, Division of  
Psychiatry Products **DATE:** September 1, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a 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).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology (OSE), we have determined that a REMS that includes elements to assure safe use is necessary for Seroquel (quetiapine fumarate) to ensure that the benefits of the drug outweigh the risks of hyperglycemia, hyperlipidemia, and weight gain associated with all forms of Seroquel (quetiapine fumarate). In reaching this determination, we considered the following:

A. The estimated number of patients in the United States with schizophrenia and bipolar disorder for which product is indicated.

Schizophrenia is a disabling psychiatric illness, affecting about 1% of the population (DSM-IV-TR, APA 2000). The typical age of onset is in the late teens to mid-20s, Loranger (1984) indicated that 39% of men and 23% of women with schizophrenia experience onset of this disorder before 19 years of age. Childhood schizophrenia is

less common than in adolescence or adulthood (AACAP 2001); with estimated prevalence in childhood of 1 in 40,000 (Nicolson and Rapoport 1999).

Bipolar disorder occurs early in life, but is relatively rare below the age of 10 in most studies. Bipolar disorder commonly occurs in adolescence or early adulthood, and retrospectively 20% to 40% of adults with bipolar disorder report onset of their symptoms during childhood (Lish et al 1994). However, large surveys of adults with bipolar disorder noted that onset before age 10 years occurred in only 0.3% to 0.5% of patients (AACAP 2007), whereas the estimated prevalence among children and adolescents aged 9 to 17 years is 1.2% (Kessler et al 1994).

#### B. Description of the seriousness of the disease of condition and impact of product use

Schizophrenia is a serious mental illness that includes disorder of thinking, disorganized behavior, deficits in cognition, affect, and social functioning. It is a chronic and debilitating illness that affects many aspects of a patient's life and has been associated with reduced life expectancy (AACAP 2001, APA 2000a, APA 2004). Adolescents with schizophrenia, like affected adults, have significant impairment, including similar thought disorder, deficits in cognition, affect, and social functioning. Childhood onset schizophrenia is a clinically severe form of schizophrenia in which the disruption in cognitive, linguistic, and social development can occur before the appearance of psychotic symptoms (Jacobsen and Rapoport 1998). Considerable distinctions have been made between adult-onset schizophrenia (AOS), adolescent or "early-onset" schizophrenia (EOS; 13-18 years old at onset), and childhood or "very early onset schizophrenia" (VEOS; < 13 years old at onset). Childhood schizophrenia is less common than in adolescence or adulthood (AACAP 2001); with estimated prevalence in childhood of 1 in 40,000 (Nicolson and Rapoport 1999). In addition, the symptomatology in childhood schizophrenia may be different from schizophrenia in adults or adolescents (Röpcke and Eggers 2005, Volkmar 1996).

Mania is an essential feature of bipolar disorder I, and is characterized by abnormally elevated, expansive, or irritable mood; accompanied by symptoms including inflated self esteem or grandiosity, decreased need for sleep, talkativeness, flight of ideas or racing thoughts, distractibility, increased goal-setting activity or psychomotor agitation, and excessive involvement in pleasurable activities; such as buying sprees, sexual indiscretions, or foolish business investments (APA 2000b). Bipolar disorder is a lifelong psychiatric illness that is characterized by significant morbidity and mortality and is often progressive (Lish et al 1994). Children and adolescents with mania, like affected adults, have significant social impairment leading to conflict within the family, repeated hospitalization, and increased economic burden on the family (Findling et al 2003, Papolos and Papolos 1999). Adolescents with bipolar disorder have an increased risk of substance-abuse disorders (Wilens et al 1999). Because bipolar disorder often manifests early in life and has been associated with poor outcomes, there is a need for early recognition of the disorder and effective treatments for young patients (Strober et al 1995, Geller et al 2002). Bipolar disorder

occurs early in life, but is relatively rare below the age of 10 in most studies. Onset of bipolar disorder commonly occurs in adolescence or early adulthood, and retrospectively 20% to 40% of adults with bipolar disorder report onset of their symptoms during childhood (Lish et al 1994). However, large surveys of adults with bipolar disorder noted that onset before age 10 years occurred in only 0.3% to 0.5% of patients (AACAP 2007), whereas the estimated prevalence among children and adolescents aged 9 to 17 years is 1.2% (Kessler et al 1994).

#### C. Potential benefit of use of product

At this time there are limited therapeutic options approved for pediatric patients with schizophrenia or mania, especially compared to the spectrum of drugs available for use in adults with the same disorders. Until August 2007, there were no FDA-approved drugs for the treatment of pediatric schizophrenia, and only lithium was approved for the treatment of bipolar disorder in adolescents ages 12 and up. Since that time, 2 atypical antipsychotic medications (risperidone and aripiprazole) have been approved in the US for treatment of both disorders in pediatric patients. Quetiapine has been approved in the US for the treatment of adult patients with schizophrenia and mania. Quetiapine tablets have been shown to reduce the signs and symptoms in adolescent patients with schizophrenia.

For adults with mania, treatment options include the mood stabilizers lithium and divalproate, and the atypical antipsychotics quetiapine, olanzapine, and aripiprazole. Conventional antipsychotics, such as haloperidol, are used to treat acute mania in adult patients, but their utility is limited because of the risk of extrapyramidal side effects (Hunt and Silverstone 1991, Kane 1988, Baldessarini et al 1988, Mukherjee et al 1986). Published studies suggest that lithium and divalproate may be effective treatments for some children and adolescents with mania, but many patients in these studies did not respond to mood-stabilizer treatment (Geller et al 2000, Kowatch et al 2000, West et al 1995). In addition, these agents require blood monitoring to maintain therapeutic levels and avoid toxicity. Lithium treatment may be associated with such adverse effects as impaired thyroid function and tremor (Freeman and Freeman 2006). Divalproate treatment may be associated with hepatotoxicity or pancreatitis (Gerstner et al 2007, Lheureux et al 2005). Quetiapine tablets have shown to reduce manic symptoms in pediatric patients with bipolar mania (aged 10 to 17 yrs).

#### D. Information on expected use of product

The expected duration of therapy with Seroquel® (quetiapine) tablets in patients who obtain a clinical response will minimally be 6 months to a year, and may be for many years; schizophrenia and bipolar disorder are considered life-long diseases, although the severity of symptoms may vary over time.

The majority of sales of Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) were to outpatient retail pharmacy settings. During year

2008, approximately (b) (4) million prescriptions were dispensed for quetiapine. Prescriptions dispensed to pediatric patients aged 0-12 years accounted for less than (b) (4) of the total dispensed prescriptions for all three agents. Adolescents aged 13-17 years accounted for approximately (b) (4) of dispensed prescriptions of quetiapine. The trends for patient data were similar to prescription data. The most common diagnosis associated with the use of the three agents is “Affective Psychoses” ICD-9 296 and “Schizophrenic Disorders” ICD-9 295. Psychiatrists were the most common prescribers for these agents.

During 2008, approximately (b) (4) million patients received a prescription for quetiapine compared to (b) (4) patients receiving olanzapine and (b) (4) receiving ziprasidone. The number of dispensed prescriptions has increased over the past 5 years.

E. Data on 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 based on available data

Several safety concerns have been identified in the adult clinical trials programs for quetiapine as well as for atypical antipsychotics in general. Known potential safety signals include weight gain, hyperlipidemia, hyperglycemia, and potential clinical worsening of suicidality (class effect associated in certain age groups). Based on the DPP review of safety data included in the pending pediatric efficacy supplements for schizophrenia and bipolar disorder under NDA-20639/S-045 and 046, the submission revealed no findings which were inconsistent with the previously observed safety profile of quetiapine IR and XR in adult clinical trials.

The current quetiapine label contains Warning language describing an association with hyperglycemia, diabetes mellitus, weight gain, and lipid elevations. The label also contains the standard box warning and other warning language regarding suicidality as it has been approved for its use in bipolar depression although quetiapine is quite different pharmacologically than other antidepressants. Suicidality has been addressed previously, through the addition of the then-standard antidepressant MedGuide to the Seroquel labeling, when Seroquel was approved for use in the treatment of bipolar depression (NDA 20-639, S-026; approval date 20 October 2006). However, this MedGuide has not been revised to address the new safety information related to hyperglycemia, hyperlipidemia, and weight gain.

In addition, the Division of Pharmacovigilance (DPV), Office of Surveillance of Epidemiology (OSE) conducted a review in response to a request from the Division of Psychiatry Products (DPP) to analyze the Adverse Event Reporting System (AERS) pediatric postmarketing data for quetiapine in patients aged 0-17 years of age since approval on September 26, 1997. The focus of the review was all pediatric cases of death, metabolic effects (blood triglycerides increased, diabetes mellitus, hyperglycemia, and weight increased), QT prolongation, and Torsade de pointes.

It was found that the safety profile of the pediatric population is very similar compared to the adult population, and the adverse events occurred in much the same manner as well. No new safety signals emerged as part of this review; however, it has made us aware that the pediatric population is not spared from the adverse events caused by quetiapine therapy. The potential risks of quetiapine therapy should be weighed against the potential benefit when choosing to initiate therapy.

F. Seroquel 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 (quetiapine fumarate). FDA has determined that Seroquel (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 (quetiapine fumarate). FDA has determined that Seroquel (quetiapine fumarate) is a product for which patient labeling could help prevent serious adverse effects.

The elements of the REMS will be a MedGuide (revisions to existing MedGuide to address the new safety information related to hyperglycemia, hyperlipidemia, and weight gain) 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-20639	SUPPL-45	ASTRAZENECA LP	SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA-20639	SUPPL-46	ASTRAZENECA LP	SEROQUEL(QUETIAPINE FUMARATE)25/100/200M

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/s/

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KIMBERLY S UPDEGRAFF  
09/02/2009

THOMAS P LAUGHREN  
09/02/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**020639Orig1s046**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



NDA 20-639/S-045/S-046

**PRIOR APPROVAL SUPPLEMENT**

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

Dear Limp:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Seroquel (quetiapine fumarate) tablets

NDA Number: 20-639

Supplement number(s): S-045/S-046

Review Priority Classification: Priority (P)

Date of supplement: October 28, 2008

Date of receipt: October 28, 2008

These supplemental applications propose new indications for the treatment of schizophrenia in adolescents (13 to 17 years of age) and bipolar disorder in children (10 to 12 years of age) and adolescents (13 to 17 years of age).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 27, 2008 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 28, 2009.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

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 questions, please call the undersigned at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Kimberly Updegraff, R.Ph., M.S.  
Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Kimberly Updegraff  
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