CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-639/S-037

Trade Name: Seroquel

Generic Name: quetiapine fumarate

Sponsor: AstraZeneca Pharmaceuticals LP

Approval Date: May 13, 2008

Purpose: Provides for the use of Seroquel as maintenance treatment for bipolar I disorder, as adjunctive therapy to lithium or divalproex

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-639/S-037

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-639/S-037

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-639 S-025, S-037, S-038, S-040

AstraZeneca Pharmaceuticals LP
Attn: Gerald Limp
Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp:

Please refer to your supplemental new drug application [sNDA] 20-639 S-037, referenced above, which was submitted and received on July 19, 2007 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) Tablets.

Please also refer to your amendments to the above referenced sNDA, submitted on October 24, 2007, October 29, 2007, November 15, 2007, November 16, 2007, and February 12, 2008.

In addition, please refer to your labeling supplements, NDA 20-639 S-025, S-038, and S-040. S-025 was submitted on November 14, 2005 and received on November 15, 2005. S-038 was submitted and received on July 30, 2007. S-040 was submitted and received on February 15, 2008, and amended on February 25, 2008.

NDA 20-639 S-037 provides for the use of Seroquel as maintenance treatment for bipolar I disorder, as adjunctive therapy to lithium or divalproex.

NDA 20-639 S-025 provides for changes in the labeling to describe the metabolite, N-desalkyl quetiapine. NDA 20-639 S-038 provides for changes in the labeling to add information about restless legs and anaphylaxis to the Adverse Events section of labeling and information on concomitant use with protease inhibitors to the Drug Interactions section of labeling. NDA 20-639 S-040 provides requested class labeling revisions pertaining to dystonia.

We have completed our review of your submissions as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling, unless we notify you otherwise.

Content of Labeling: Structured Product Labeling [SPL]. the final printed labeling (FPL) must be identical to the enclosed labeling [package insert], and must be formatted in accordance with the requirements of 21 CFR 201.66.

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)] in structured Product Labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html , that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "SPL for approved NDA labeling under NDA 20-639 S-037".

Pediatric Research Equity Act (PREA) Requirements: Phase 4 Commitments.
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years because:

A) necessary studies are impossible or highly impracticable. This is because bipolar disorder cannot be reliably diagnosed in this age group, and therefore appropriate studies cannot be developed and carried out.

We are deferring submission of your pediatric studies for ages 10 to 17 years because:

B) pediatric studies should be delayed until additional safety or effectiveness data have been collected. We are aware that submission of pediatric studies under your existing Written Request is imminent, and these studies, once reviewed, may be sufficient to address the PREA requirement for this indication.

The deferred studies should be submitted by ***June 1, 2015.***

There are no other Phase 4 commitments or Phase 4 requirements for this submission.

"Dear Healthcare Professional" Letters.
If you issue a letter communicating important information about this product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA, with a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Introductory Promotional Materials.
In addition, submit three copies of the introductory promotional materials that you propose to use for this indication. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

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

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

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-796-1040.

Sincerely,

{See appended electronic signature page}

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

Enclosure: agreed-upon labeling.

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

/s/

Thomas Laughren
5/13/2008 10:49:19 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-639/S-037

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.***

- **Atypical 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----------

WARNING: Suicidality and Antidepressant Drugs *(see Boxed Warning*) 06/2007
Warnings and Precautions, Suicidality and Antidepressant Drugs (5.2) 06/2007
Warning: Hyperglycemia and Diabetes Mellitus (5.3), 06/2007
Warnings and Precautions, Leukopenia, Neutropenia, and Agranulocytosis (5. 6) 11/2007
Indications and Usage, Bipolar Disorder (1.1) 05/2008
Dosage and Administration, Bipolar Disorder (2.1) 05/2008

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

SEROQUEL is an atypical antipsychotic agent indicated for Bipolar Disorder including: Bipolar Depression (1.1), Bipolar Mania (1.1), Bipolar Maintenance (1.1), and Schizophrenia (1.2)

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

Bipolar Depression: administered once daily at bedtime to reach 300 mg/day by day 4 (2.1)

Bipolar Mania: should be initiated in bid 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 bid divided doses (2.1)

Bipolar Maintenance: Continue treatment at the dosage required to maintain symptom remission. (2.1)

Schizophrenia: initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid (2.2)

---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)
- **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 DM risk factors should undergo blood glucose testing before and during treatment. (5.3)
- **Neuroleptic Malignant Syndrome (NMS):** Potentially fatal symptom complex has been reported with antipsychotic drugs, including quetiapine. (5.4)
- **Orthostatic Hypotension:** Associated dizziness, tachycardia and syncope especially during the initial dose titration period. (5.5)
- **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 leucopenia/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 (5.6)
- **Tardive Dyskinesia** may develop acutely or chronically (5.7)
- **Cataracts**: Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination should be done when starting treatment and at 6-month intervals during chronic treatment. (5.8).
- **Hyperlipidemia** (5.11)
- The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. (5.18)
- See Full Prescribing Information for additional **WARNINGS and PRECAUTIONS.**

----------ADVERSE REACTIONS-------

Most common adverse reactions (incidence ≥5% and twice placebo): dry mouth, sedation, somnolence, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, weight gain, lethargy, hyperglycemia, nasal congestion, SGPT increased, dyspepsia, (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 have not been established. (8.4)

--------SEE 17 FOR PATIENT COUNSELING INFORMATION

Revised 05/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

Bipolar Maintenance

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

Warning: **Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen 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 (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SEROQUEL (quetiapine) is not approved for the treatment of patients with Dementia-Related Psychosis.

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 pediatric patients. *[See Warnings and Precautions (5.2)]*

1 INDICATIONS AND USAGE

1.1 Bipolar Disorder

SEROQUEL is indicated for the treatment of:

- depressive episodes associated with bipolar disorder
- acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex.
- maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex.

Depression

The efficacy of SEROQUEL was established in two identical 8-week randomized, placebo-controlled double-blind clinical studies that included either bipolar I or II patients [*see Clinical Pharmacology(12*)]. Effectiveness has not been systematically evaluated in clinical trials for more than 8 weeks.

Mania

The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania [s*ee Clinical Pharmacology (12)*]. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy.

Maintenance Treatment in Bipolar Disorder

The efficacy of SEROQUEL as adjunct maintenance therapy to lithium or divalproex was established in 2 identical randomized placebo-controlled double-blind studies in patients with Bipolar I Disorder. [*see Clinical Studies (14)*]

The physician who elects to use SEROQUEL for extended periods in Bipolar Disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient [*see Dosage and Administration (2)*].

1.2 Schizophrenia

SEROQUEL is indicated for the treatment of schizophrenia.

The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients [*see Clinical Pharmacology (12)*].

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-

evaluate the long-term usefulness of the drug for the individual patient [*see Dosage and Administration (2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Bipolar Disorder

Depression

Usual Dose: 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.

Mania

Usual Dose: When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL should be initiated in bid 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 bid 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 to 800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Maintenance

Maintenance of efficacy in Bipolar I Disorder was demonstrated with SEROQUEL (administered twice daily totalling 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)*].

2.2 Schizophrenia

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. 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 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg twice per day was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 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 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

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 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

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

2.4 Maintenance Treatment

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.

2.5 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.

2.6 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 reevaluated 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 atypical antipsychotic drugs are at an increased risk of death compared to placebo. 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

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
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 health care 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 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 [See *Adverse Reactions, hyperglycemia (6.1)*]. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for

hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available.

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

5.4 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.

5.5 Orthostatic Hypotension

SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_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.

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). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid [s*ee 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.

5.6 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/mm^3) should discontinue SEROQUEL and have their WBC followed until recovery (See ADVERSE REACTIONS).

5.7 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. 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 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 patients 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.

5.9 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.

5.10 Hypothyroidism

Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients and levels of 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.

5.11 Cholesterol and Triglyceride Elevations

In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol ≥240 mg/dL and triglycerides ≥200 mg/dL were 16% and 23% for SEROQUEL treated patients respectively compared to 7% and 16% for placebo patients respectively. In bipolar depression trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 9% and 14% for SEROQUEL treated patients respectively, compared to 6% and 9% for placebo patients respectively.

5.12 Hyperprolactinemia

Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats [*see Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)]*. 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 contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. 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; the available evidence is considered too limited to be conclusive at this time.

5.13 Transaminase Elevations

Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, 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% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, 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 and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with 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% for SEROQUEL and 2% for placebo.

5.14 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% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% 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% of patients on SEROQUEL compared to 9% of placebo patients. In bipolar depression trials, somnolence was reported in 28% of patients on SEROQUEL compared to 7% of placebo patients. In these trials, sedation was reported in 30% of patients on SEROQUEL compared to 8% 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.

5.15 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.

5.16 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.

5.17 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.

5.18 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%).

5.19 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 (5.5)*].

5.20 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

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, ~~and~~ 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.

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

Bipolar Disorder:

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.

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.

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 and hypotension were considered to be drug related: [s*ee Warnings and Precautions (5)*]

Adverse Event	**SEROQUEL**	**Placebo**
Somnolence	0.8%	0%
Hypotension	0.4%	0%

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 2 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 2. Treatment-Emergent Adverse Reaction Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (monotherapy)[1]

Body System/ Preferred Term	**SEROQUEL (n=719)**	**PLACEBO (n=404)**
Body as a Whole		

Headache	21%	14%
Pain	7%	5%
Asthenia	5%	3%
Abdominal	4%	1%
Back Pain	3%	1%
Fever	2%	1%
Cardiovascular		
Tachycardia	6%	4%
Postural Hypotension	4%	1%
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%
SGPT Increased	5%	1%
SGOT 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%
Special Senses		
Amblyopia	2%	1%

[1] 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 these 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 (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%).

Table 3 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 5% 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 3. Treatment-Emergent Adverse Reaction Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy)[1]

Body System/ Preferred Term	**SEROQUEL (n=196)**	**PLACEBO (n=203)**
Body as a Whole		
Headache	17%	13%
Asthenia	10%	4%
Abdominal Pain	7%	3%
Back Pain	5%	3%
Cardiovascular		
Postural Hypotension	7%	2%
Digestive		
Dry Mouth	19%	3%
Constipation	10%	5%
Metabolic and Nutritional		
Weight Gain	6%	3%
Nervous		

Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
Respiratory		
Pharyngitis	6%	3%

[1] 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, and nausea.

In these 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 4 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 5% 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 4. Treatment-Emergent Adverse Reaction Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression[1]

Body System/ Preferred Term	**SEROQUEL (n=698)**	**PLACEBO (n=347)**
Gastrointestinal Disorders		
Dry Mouth	44%	13%
Constipation	10%	4%
Dyspepsia	7%	4%
Vomiting	5%	4%
General Disorders and Administrative Site Conditions		
Fatigue	10%	8%
Metabolism and Nutrition Disorders		

Increased Appetite	5%	3%
Nervous System Disorders		
Sedation	30%	8%
Somnolence	28%	7%
Dizziness	18%	7%
Lethargy	5%	2%
Respiratory, Thoracic, and Mediastinal Disorders		
Nasal Congestion	5%	3%

[1]Events 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, and headache.

In these 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 dry mouth (44%), sedation (30%), somnolence (28%), dizziness (18%), constipation (10%), lethargy (5%), and nasal congestion (5%).

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.

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.

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.

SEROQUEL

Dose Groups	**Placebo**	**75 mg**	**150 mg**	**300 mg**	**600 mg**	**750 mg**
Parkinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS incidence	16%	6%	6%	4%	8%	6%
Anticholinergic medications	14%	11%	10%	8%	12%	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.

Vital Signs and Laboratory Studies

Vital Sign Changes

SEROQUEL is associated with orthostatic hypotension [*see Warnings and Precautions (5.6)*].

Weight Gain

In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% compared to 2% for placebo.

Laboratory Changes

An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been observed. [*see Warnings and Precautions (5.11)*].

In placebo controlled monotherapy clinical trials involving 3368 patients on SEROQUEL and 1515 on placebo, the incidence of at least one occurrence of neutrophil count <1.0 x 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 SEROQUEL, compared to 0.1% (2/1349) in patients treated with placebo. [*See Warnings and Precautions (5.6)]*

ECG Changes

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 may be related to SEROQUEL's potential for inducing orthostatic changes [*see Warnings and Precautions (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 ≥ 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: ***Frequent:*** hypertonia, dysarthria; ***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: ***Frequent****:* palpitation; ***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****:* pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent****:* pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation.

Metabolic and Nutritional System: ***Frequent****:* peripheral edema; ***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: ***Frequent****:* sweating; ***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: ***Frequent:*** leukopenia; ***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 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, restless legs, and leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia.

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

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 tid) and phenytoin (100 mg tid) 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 bid) and divalproex (500 mg bid) 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 bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

*Cimetidine***:** Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). 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 bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) 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 tid 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 bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant.

Lithium: Concomitant administration of quetiapine (250 mg tid) 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 tid 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

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^2 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^2 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^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human

dose on a mg/m^2 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^2 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^2 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^2 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^2 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

The safety and effectiveness of SEROQUEL in pediatric patients have not been established. Anyone considering the use of SEROQUEL in a child or adolescent must balance the potential risks with the clinical need.

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 (5.6)*]. 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

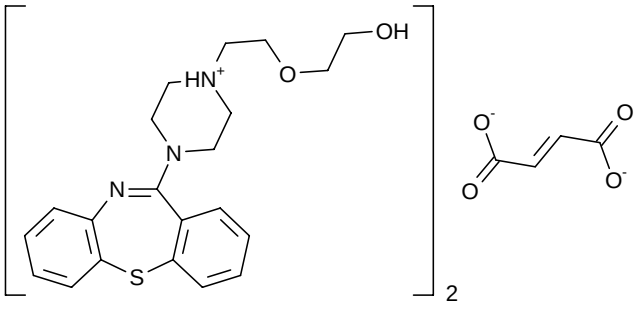
In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or 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® (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 $C_{42}H_{50}N_6O_4S_2 \bullet C_4H_4O_4$ 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 α_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 α_1 and α_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

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.

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±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination

Following a single oral dose of ^{14}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 (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary [s*ee 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 (Clcr=10-30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (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_{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 [s*ee 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)*].

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^2 basis (mice) or 0.3, 0.9,

and 3.0 times the maximum human dose on a mg/m^2 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^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 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^2 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-yr 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 (5.11)*].

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^2 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^2 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^2 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^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 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^2 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^2 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^2 basis.

14 CLINICAL STUDIES

14.1 Bipolar Disorder

Depression

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

The primary rating instrument used to assess depressive symptoms in these studies was the 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).

Mania

The efficacy of SEROQUEL in the treatment of acute 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 treatment of bipolar maintenance 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 and 800 mg per day.

Adjunct Therapy

In this 3-week placebo-controlled trial, 170 patients with acute bipolar mania (YMRS ≥ 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 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**.**

Maintenance Therapy

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 totalling 400 to 800 mg per 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 both manic and depressed episodes. The effect of SEROQUEL was independent of any specific subgroup (assigned mood stabilizer, sex, age, race, most recent bipolar episode, or rapid cycling course).

14.2 Schizophrenia

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. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

1. In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a tid schedule), 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 to 750 mg/day

were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

2. In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

3. In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

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 compared to those older than 40. The clinical significance of this finding is unknown.

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 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [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.

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.

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.

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.

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 be monitored.

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing) especially during the period of initial dose titration, and also at times of re-initiating treatment or increases in dose.

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 (5.6)*]

Interference with Cognitive and Motor Performance

Patients should be advised of the risk of somnolence or sedation, 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.

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.

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.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

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Wilmington, DE 19850
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Medication Guide
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**
• all risks and benefits of treatment with antidepressant medicines
• all treatment choices for depression or other serious mental illness

What is the most important information I should know about 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) 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 a 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 takes. 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.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-639/S-037

CROSS DISCIPLINE TEAM LEADER REVIEW

Team Leader Review Memo

Date	May 2, 2008
From	Robert Levin, M.D.
Subject	Team Leader Review
NDA/Supplement #	20-639-037
Proprietary/Established Name	Quetiapine Seroquel IR
Drug Class	Atypical Antipsychotic
Dosage forms/Strengths	Oral tablets;
Proposed Indication	Maintenance Treatment in Bipolar Disorder
Recommended:	Approval

1. Introduction and Background

The sponsor seeks an indication for quetiapine (Seroquel) as adjunctive therapy with mood stabilizers (lithium or valproate) in the maintenance treatment of Bipolar I Disorder. Currently, quetiapine is approved for two acute indications in Bipolar Disorder: 1) as monotherapy or adjunct therapy with lithium or valproate in acute mania (approved in January, 2004); and 2) as monotherapy in Bipolar depression (approved in October, 2006). For mania, quetiapine dosing is 400-800 mg, administered in divided doses twice daily. For Bipolar depression, dosing is 300-600 mg administered once daily.

On June 4, 2003, the Division met with the sponsor for an End of Phase 2 meeting to discuss proposed long-term, controlled maintenance studies of quetiapine as adjunctive therapy to mood stabilizers (lithium or valproate) in Bipolar I Disorder. The sponsor proposed two essentially identically designed placebo-controlled, randomized withdrawal studies (Studies D1447C00126 and D1447C00127). The Division indicated that a single positive maintenance trial could support a claim for quetiapine as adjunctive maintenance treatment in Bipolar Disorder. The Division recommended that the sponsor designate relapse of any event (manic, mixed, or depressed) as the primary endpoint in the survival analysis.

2. CMC

There are no unresolved CMC issues.

3. Nonclinical Pharmacology/Toxicology

There are no unresolved Pharmacology/Toxicology issues.

4. Clinical Pharmacology/Biopharmaceutics

There are no new clinical pharmacology data in this application. In previous 20-639 applications, the sponsor has documented that there are no clinically significant pharmacokinetic interactions between quetiapine and lithium or valproate. Current labeling includes relevant language.

In the action for this supplemental NDA, the Division will include actions for labeling supplements SLR-025 (submitted on November 14, 2005) and SLR-038 (submitted July 30, 2007), which include: 1) language describing the active metabolite, N-desalkyl quetiapine; and 2) language describing drug interaction with protease inhibitors and the need for reduced quetiapine dosage when used concomitantly. Kofi A. Kumi Ph.D. (Office of Clinical Pharmacology) has reviewed the supplements, and he agrees that the sponsor's proposed language regarding the quetiapine metabolite and drug-drug interaction with protease inhibitors is acceptable. These changes have been incorporated in labeling for this NDA supplement.

5. Clinical and Statistical

The sponsor conducted two identically designed placebo-controlled, randomized withdrawal studies to evaluate the efficacy of quetiapine in maintenance treatment of Bipolar I Disorder. Study 126 was conducted in Europe (128 sites), U.S. (37 sites), Australia (10 sites), and South Africa (2). Study 127 was conducted in the U.S. (86 sites) and Canada (16 sites)

5.1 Objective of the Studies

The primary objective of both studies was to evaluate the efficacy of quetiapine versus placebo when used as adjunct with lithium or valproate in increasing the time to relapse of any mood episode (depressed, manic, or mixed).

5.2 Definition of Relapse

Relapse of a mood event was appropriately defined as the occurrence of one of the following events:

1. Initiation of an antipsychotic, antidepressant, mood stabilizer other than the assigned mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a manic, depressed, or mixed event
2. hospitalization for a manic or depressed or mixed event
3. YMRS score $\geq$20 at 2 consecutive assessments or at the final assessment if the subject discontinues; or MADRS score $\geq$20 at 2 consecutive assessments or at the final assessment if the subject discontinues
4. Discontinuation from the study if, in the opinion of the investigator, the discontinuation is due to a manic, depressed, or mixed event.

5.3 Subject Selection

Inclusion criteria for entry into the open-label stabilization phase:

- (Bipolar I Disorder**)**
- A current manic, depressed, or mixed episode; with or without psychotic features; with or without rapid cycling
- Or clinically stable, with a documented past manic, depressed, or mixed episode within 26 weeks of entry into the study.
- Subjects could have entered the study untreated with psychotropic drug or treated with quetiapine, other antipsychotics, mood stabilizers, or antidepressants

5.4 Study Design

Studies 126 and 127 were essentially identically designed, double-blind, placebo-controlled, randomized withdrawal studies in subjects with Bipolar I Disorder (acutely ill or clinically stable). During the first phase of the study (7 days), subjects began treatment with quetiapine plus lithium or valproate, if they were not already treated with these drugs upon entry. The decision about which mood stabilizer to use for an individual subject was at the discretion of the investigator. "Other antipsychotic and psychoactive medications (eg, antidepressants and anxiolytics) could also be used as clinically indicated during this phase, with exception of the last 12 weeks prior to randomization."

Quetiapine was initiated at 100 mg/day on Day 1 and was increased to 400 mg/day by Day 4 in increments of 100 mg/day. The dose could then be increased to 600 mg/day on Day 5. During the open-label stabilization phase, the recommended target dosage of quetiapine was 600 mg/day, but the prescribed dosage could be adjusted within the range of 400 to 800 mg/day to maximize efficacy and tolerability. The duration of the open-label stabilization period was 12 to 36 weeks. Dose regimen and dose adjustment for lithium or valproate were at the discretion of the investigator to achieve symptom control, to minimize side effects, and to achieve target trough serum concentrations of 0.5 mEq/L to 1.2 mEq/L for lithium and 50 mic/ml to 125 mic/ml for valproate during the entire length of the study.

To be eligible to enter the placebo-controlled, randomized withdrawal study, subjects must have been treated with quetiapine within the range of 400 to 800 mg/day and mood stabilizer (lithium or valproate) for at least 12 weeks during the open-label treatment phase. To be randomized, subjects must have had a YMRS total score $\leq$ 12, and a MADRS total score $\leq$ 12 during at least 4 consecutive visits spanning at least 12 weeks, with the allowance of a single excursion with a YMRS and/or MADRS total score of 13 or 14 (unless this occurred on the last of the 4 consecutive visits).

Randomized Withdrawal Phase:

The mean duration of treatment during the open-label phase was 14-16 days in the two studies. Starting at the day of randomization, open-label 100-mg quetiapine tablets were replaced with 100-mg tablets of blinded investigational product at a rate of 1 tablet twice daily every 2 days. The rate of replacement could be slowed to increase tolerability. Replacement of quetiapine with blinded product had to be completed within 14 days (or 15 days for 800 mg/day). The dose of blinded drug could be increased as clinically indicated to a maximum of 8 tablets/day (800 mg/day) (blinded and open-label medication combined). After all open-label tablets were replaced, the dose of blinded drug (quetiapine or placebo) was adjusted as clinically indicated within the dose range of 400 to 800 mg/day.

5.5 Efficacy Findings

5.5.1 Baseline Features

The table below illustrates some of the baseline features upon randomization into the placebo-controlled study. The baseline features were similar between the placebo and quetiapine groups. However, the baseline MADRS score was higher in the placebo group, and a higher proportion of subjects had a rapid cycling course, compared to the quetiapine group.

Baseline Features			
		Placebo	Quetiapine
YMRS at enrollment	Mean median	14 13	12 10
MADRS at enrollment	Mean Median	19 19	15 12
Assigned stabilizer	Lithium valproate	40% 57%	42% 58%
Diagnosis most recent	Manic Depressed mixed	30% 34% 37%	37% 30% 34%
Rapid cycling	Unknown No yes	1% 56% 44%	0.4% 63% 37%
Time before enrollment	Mean median	78 45	73 44

5.5.2 Primary Efficacy Results

Treatment with quetiapine (400-800 mg/day) significantly delayed the time to relapse of any mood event ($p < 0.0001$). Furthermore, the proportions of subjects in the quetiapine group who had any mood episode or a relapse of depression, manic, or mixed episode was significantly smaller than those in the placebo group.

Table 1 Primary Analysis: Cox-proportional Hazard Analysis of Time to Mood Event

	QTP+LI/VAL vs. PLA+LI/VAL	
	Study 126	**Study 127**
Hazard Ratio (HR)	0.28	0.32
95% CI for HR	(0.21, 0.37)	(0.24, 0.42)
p-value	<0.001	<0.001

Source: Clinical Study Report D1447C00126, Table 24 (pg 143); Clinical Study Report D1447C00127 Table 24 (pg 143)

Table 2 Summary of Subjects with Mood Event and Censored Patients

	Study 126		Study 127	
	QTP+LI/VAL	**PLA+LI/VAL**	**QTP+LI/VAL**	**PLA+LI/VAL**
Total number of patients	336 (100%)	367 (100%)	310 (100%)	313 (100%)
Patients who had mood event	62 (18.45%)	180 (49.05%)	63 (20.32%)	163 (52.08%)
Depressed	23 (6.85%)	63 (17.17%)	30 (9.68%)	70 (22.36%)
Manic	29 (8.63%)	71 (19.35%)	16 (5.16%)	39 (12.46%)
Mixed	10 (2.98%)	46 (12.53%)	17 (5.48%)	54 (17.25%)

Source: George Kordzakhia, Ph.D.

Statistical Reviewer's Findings

George Kordzakhia, Ph.D. performed the statistical review, and he confirmed the sponsor's efficacy findings. In studies 126 and 127, quetiapine treatment (400 to 800 mg daily) was statistically significantly superior to placebo treatment, with respect to time to mood event when used as adjunct with a mood stabilizer (lithium or valproate). The p-values obtained from Cox-proportional hazard model were < 0.001.

For Study 126 the estimated hazard ratio (quetiapine versus placebo) was 0.28 (95% CI = 0.21 to 0.37, p-value <0.0001), corresponding to a hazard rate reduction of 72%. For Study 127, the estimated hazard ratio (quetiapine versus placebo) was 0.32 (95% CI = 0.24 to 0.42, p<0.0001), corresponding to a hazard rate reduction of 68%. For both studies, Kaplan Meier curves for time to recurrence of a mood event support that the mood event rate was lower in the quetiapine treatment group than in placebo treatment group during the entire randomized treatment phase.

Dr. Kordzakhia notes: "The sponsor wants to claim statistical significance of quetiapine on secondary endpoints: time to manic event and time to depressed event. However, the studies were not designed to collect time to first manic event and first depressed event separately. The primary efficacy endpoint (time to mood event) is a composite endpoint, defined as time to manic, depressed or mixed episode, whichever comes first. If a patient has a mood event due to a depressed episode, the time to first manic event would need to be censored on the date of the depressed episode and vice versa. Because of this issue, the results on these individual components as key secondary endpoints are difficult to interpret." Nevertheless, there appears to be a treatment effect for quetiapine in decreasing the risk of relapse of each type of mood event (depressed, manic, or mixed).

As demonstrated by subgroup analyses, the quetiapine treatment effect (as measured by the hazard ratio (HR) was consistent across subgroups defined by the following: 1) type of index episode (manic/mixed/depressed); 2) assigned mood stabilizer (lithium/valproate); 3) presence or absence of rapid cycling course; 4) demographic characteristics (gender, age, race); 5) geographic region (North America vs. Rest of World).

6 Safety Findings

6.1 Exposure

The total quetiapine exposure during the combined open-label treatment phase and randomized treatment phase was 1,342 person-years in Studies 126 and 127. Among the 1,326 subjects in the randomized safety population, 725 (55%) were exposed to quetiapine for >26 weeks (open-label plus controlled phase), and 273 (21%) were exposed to quetiapine for >52 weeks. During the randomized treatment phase, the quetiapine exposure in the lithium subgroup was 166 person-years, and the quetiapine exposure in the valproate subgroup was 209 person-years.

6.2 Adverse Events: Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events, and Common Adverse Events

There were no new or unexpected adverse events with quetiapine in the maintenance studies. Generally, the safety profile of quetiapine in the maintenance study was similar to that observed in previous studies with quetiapine. Quetiapine was reasonably safe and well tolerated in the maintenance studies in subjects with Bipolar Disorder

During the open-label phase of studies 126 and 127, three subjects treated with quetiapine completed suicide, and one subject treated with quetiapine died from pneumonia. (One of the suicides occurred 90 days after the last dose of quetiapine). During the placebo-controlled phase, two subjects with quetiapine completed suicide, and three subjects in the placebo group died (suicide, cardiac failure, and unknown cause). During the placebo-controlled phase, the two suicides in the quetiapine group occurred 24 and 25 days after the last dose of quetiapine. None of the deaths in the quetiapine group appear to have been related to treatment with quetiapine.

During the placebo-controlled trial, there were 22 (3.4%) subjects with serious adverse events, compared to 27 (3.9%) in the placebo group. The most common serious adverse events in the quetiapine group were depression (2) and suicidal ideation (2). Two cases were probably related to treatment with quetiapine (extrapyramidal symptoms and hyperglycemia).

Discontinuations due to adverse events were more common in the quetiapine group (6.7%) than in the placebo group (3.4%). Adverse events leading to discontinuation that were probably or possibly related to treatment with quetiapine included: weight gain

(2%), sedation (1%), hyperglycemia (1%), and extrapyramidal symptoms (0.3%), hypothyroidism, and neutropenia.

Adverse events that were probably related to treatment with quetiapine included: sedation, extrapyramidal symptoms, weight gain, hypothyroidism, and hyperglycemia. There were two cases of cataracts that were possibly related to treatment with quetiapine. Treatment with quetiapine was associated with decreases in thyroxine concentrations and increases in thyroid stimulating hormone. Such changes are known to occur with quetiapine treatment.

7Labeling

The Division has been in the process of discussing proposed labeling with the sponsor. At this point, we are in agreement about labeling for Seroquel IR, including specific language about the controlled maintenance studies.

8. DSI Audits

There were no special concerns at the 2 sites inspected for this application. The sites were chosen for inspection, because they were high enrollers. The DSI reviewers concluded that, except for minor deficiencies at each site, the investigators adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. The DSI summary was prepared by Dianne Tesch, Consumer Safety Officer and Tejashri Purohit-Sheth, M.D., Acting Branch Chief Good Clinical Practice Branch II, Division of Scientific Investigations Office of Compliance

9. Conclusions and Recommendations

9.1 Recommended Regulatory Action

I recommend that the Division take an approval action for this supplemental NDA. In two adequate and well controlled trials, the sponsor demonstrated that quetiapine (as adjunctive treatment with mood stabilizers) significantly delayed the time to relapse of a mood event in Bipolar I Disorder. The treatment effect was statistically and clinically significant. Furthermore, adjunctive treatment with quetiapine was reasonably safe and well tolerated. There were no new or unexpected safety issues with quetiapine treatment in these studies.

9.2 Postmarketing Studies (under PREA, Subpart H)

At this point, the Division plans to defer the requirement for the sponsor to conduct a placebo-controlled maintenance study of quetiapine in pediatric subjects with Bipolar Disorder. The sponsor plans to submit the results of pediatric studies in acute mania. If the results of the acute mania studies are positive, the Division would consider waiving

the requirement for a pediatric Bipolar maintenance study, since one could extrapolate efficacy in maintenance treatment from the results of the adult maintenance studies.

Robert L. Levin, M.D., May 6, 2008
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: NDA 20-639
HFD 130
T Laughren
M Mathis
E Hearst
D Bates

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

/s/

Robert Levin
5/6/2008 03:54:23 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-639/S-037

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 20-639
Submission Number	SE1-037
Submission Code	N
Letter Date	09/17/2007
Stamp Date	09/17/2007
PDUFA Goal Date	05/19/2008
Reviewer Name	Earl D. Hearst, M.D.
Review Completion Date	03/31/2008
Established Name	quetiapine fumarate
Trade Name	Seroquel
Therapeutic Class	Atypical Antipsychotic
Applicant	AstraZeneca
Priority Designation	S
Formulation	tablet
Dosing Regimen	400-800 mg/day
Indication	maintenance treatment of bipolar I disorder, as adjunct therapy to lithium or valproate
Intended Population	Adults

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend that we approve Seroquel for maintenance treatment of bipolar I disorder, as adjunct therapy to lithium or valproate.

1.2 Recommendation on Postmarketing Actions

I have no recommendations.

1.2.1 Risk Management Activity

I have no recommendations.

1.2.2 Required Phase 4 Commitments

I have no recommendations.

1.2.3 Other Phase 4 Requests

I have no recommendations.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This clinical program deals with the efficacy and safety of quetiapine when used as adjunct with lithium or valproate in the maintenance treatment of patients with bipolar I disorder. The program consisted of 2 Phase III studies (Study 126 and Study 127) that were virtually identical in design with only a few differences (see sec. 6.1.1).

1.3.2 Efficacy

Studies 126 and 127 were statistically superior to placebo ($p < .001$) with respect to time to mood event when used as adjunct with a mood stabilizer (lithium or valproate).

1.3.3 Safety

There are no new or unusually safety patterns in this submission that differ from the current label.

1.3.4 Dosing Regimen and Administration

Dosing in these studies with quetiapine was initiated at 100 mg/day on Day 1 and was increased to 400 mg/day on Day 4 in increments of 100 mg/day. The dose could then be increased to 600 mg/day on Day 5. The recommended target dosage of quetiapine was 600 mg/day, but the prescribed dosage could be adjusted within the range of 400 to 800 mg/day to maximize efficacy and tolerability.

1.3.5 Drug-Drug Interactions

The absence of a clinically relevant pharmacokinetic interaction between quetiapine and lithium and between quetiapine and valproate is already noted in the current prescribing information for quetiapine.

1.3.6 Special Populations

The incidence of common AEs in patients with bipolar I disorder who received quetiapine as adjunct with lithium or valproate was generally consistent across mood stabilizer, age, sex, and race with minor exceptions noted in section 7.4.2.3.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Approval is being sought for the use of quetiapine fumarate (SEROQUEL™, quetiapine) in the maintenance treatment of bipolar I disorder, as adjunct therapy to lithium or valproate. Currently approved indications in the United States (US) include the acute treatment of bipolar disorder as follows:

Mania, 400 mg/day to 800 mg/day, administered twice daily, as monotherapy or as adjunct therapy with lithium or valproate (approved in January 2004); and

Bipolar depression, 300 mg and 600 mg once daily as monotherapy (approved in October 2006).

2.2 Currently Available Treatment for Indications

There are many similar drugs used off label for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

Seroquel is approved and available.

2.4 Important Issues With Pharmacologically Related Products

There are no important issues relevant to this submission..

2.5 Presubmission Regulatory Activity

The 6/4//2003 End of Phase 2 meeting was held between AstraZeneca and the Division of Psychiatry Products to discuss AstraZeneca's proposed program for long-term maintenance treatment in bipolar disorder, using SEROQUEL solely as an adjunct to mood stabilizer therapy (Studies D1447C00126 and D1447C00127). The key agreements were:

The Division indicated that these trials could support a claim for quetiapine as adjunctive treatment for increased time to relapse.

FDA noted that a single positive maintenance trial would be sufficient, if the acute studies in mania were judged to be positive.

FDA recommended that AstraZeneca focus on any mood event as the primary endpoint,

1/8/ 2007 AstraZeneca submitted responses to the FDA's 12 December 2006 clinical and statistical feedback on the statistical analysis plans by email as follows:

The proportional hazards model will be used in the primary analysis.

The clinical objective of including the rating scales is to examine the effectiveness in suppressing symptoms during the maintenance phase.

Adverse events emerging during the randomized treatment phase will be the primary approach.

If an adverse event is missing dates, a worst-case scenario will be assumed and the date will be set to the same date as start of study medication.

Triglycerides will not be excluded in the presentation of metabolic risk factors.

Preferred terms, verbatim terms and comments in the appropriate fields will be included in the Columbia suicidality analysis per the FDA's recommendations.

Patients will be stable for 12 consecutive weeks to be eligible for randomization. Any data collected during this stabilization period should be suitable baseline data.

2.6 Other Relevant Background Information

I have no comments.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Since there was no new information to be included in the CMC (chemistry, manufacturing, and control), preclinical, or pharmacokinetic sections of this sNDA, Modules 2.3 (Quality Overall Summary), 2.4 (Nonclinical Overview), 2.6 (Nonclinical Summary), 2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods), 2.7.2 (Summary of Clinical Pharmacology Studies), 3 (Quality), and 4 (Nonclinical Study Reports) are cross-referenced to NDA 20-639 and associated supplements.

3.2 Animal Pharmacology/Toxicology

See above.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

4.2 Tables of Clinical Studies

TABULAR LISTING OF ALL CLINICAL STUDIES

Type of study	Study identifier	Primary objective of the study	Study design and types of control	Test product(s); Dosage regimen; Route of admin.	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type and location of study report	Site location (number of centers)
Safety and efficacy	D1447C00126 (126)	To evaluate the efficacy of quetiapine versus placebo when used as adjunct with lithium or valproate in increasing time to recurrence of a mood event	Multicenter, double-blind, randomized, parallel-group, placebo-controlled study with open-label stabilization run-in phase	Quetiapine twice daily by mouth, total daily dose 400 - 800 mg; Adjunct therapy target trough serum concentrations: 0.5 mEq/L to 1.2 mEq/L for lithium and 50 µg/ml to 125 µg/ml for valproate	706 patients randomized (710 planned)	Bipolar I Disorder (DSM-IV); most recent episode manic, depressed, or mixed; with or without psychotic features	12 to 36 weeks of open-label treatment with quetiapine; up to 104 weeks of double-blind treatment with quetiapine or placebo	Completed; Full report included in this submission (Module 5.3.5.1)	Europe (128), US (37), Australia (10), South Africa (2)
Safety and efficacy	D1447C00127 (127)	To evaluate the efficacy of quetiapine versus placebo when used as adjunct with lithium or valproate in increasing time to recurrence of a mood event	Multicenter, double-blind, randomized, parallel-group, placebo-controlled study with open-label stabilization run-in phase	Quetiapine twice daily by mouth, total daily dose 400 - 800 mg; Adjunct therapy target trough serum concentrations: 0.5 mEq/L to 1.2 mEq/L for lithium and 50 µg/ml to 125 µg/ml for valproate	628 patients randomized (710 planned)	Bipolar I Disorder (DSM-IV); most recent episode manic, depressed, or mixed; with or without psychotic features	12 to 36 weeks of open-label treatment with quetiapine; up to 104 weeks of double-blind treatment with quetiapine or placebo	Completed; Full report included in this submission (Module 5.3.5.1)	US (86), Canada (16)

4.3 Review Strategy

My review will center on the two pivotal studies.

4.4 Data Quality and Integrity

The data quality and integrity are adequate and sufficient for the review.

4.5 Compliance with Good Clinical Practices

All SEROQUEL® clinical studies utilize good clinical practices (GCP) in compliance with the Institutional Review Board (IRB) requirements in 21 CFR 56, and informed consent requirements in 21 CFR 50.

4.6 Financial Disclosures

There were no problems with financial disclosures.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The pharmacokinetics program for quetiapine was provided in previously approved registration dossiers (NDA 20-639). A lack of clinically significant pharmacokinetic interactions with lithium and with valproate is documented in the approved label.

5.2 Pharmacodynamics

The pharmacodynamics program for quetiapine was provided in previously approved registration dossiers (NDA 20-639).

5.3 Exposure-Response Relationships

The two submitted studies explored a flexible dose of 400-800mg of Seroquel.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Approval is being sought for the use of quetiapine fumarate (SEROQUEL™, quetiapine) in the maintenance treatment of bipolar I disorder, as adjunct therapy to lithium or valproate.

6.1.1 Methods

This clinical program deals with the efficacy and safety of quetiapine when used as adjunct with lithium or valproate in the maintenance treatment of patients with bipolar I disorder. The program consisted of 2 Phase III studies (Study 126 and Study 127) that were virtually identical in design with only a few differences (Table E- 1).

Sponsor Table E- 1 Differences in design between Study D1447C00126 and Study D1447C00127

Study D1447C00126	Study D1447C00127
Sleep medications permitted: Zolpidem tartate 10 mg; Zaleplon 20 mg; Zopiclone 7.5 mg; chloral hydrate 1 g	Sleep medication permitted: Zolpidem tartrate 10 mg
Lorazepam 2 mg or lorazepam substituted with oxazepam 30 mg in Australia, Czech Republic, and Norway or alpazoram 0.5 mg in Hungary	Lorazepam 2 mg
Conducted in Australia, Belgium, Bulgaria, Czech Republic, Finland, France, Germany, Hungary, Italy, Norway, Poland, Russia, Spain, Sweden, Turkey, UK, US, South Africa	Conducted in US and Canada

6.1.2 General Discussion of Endpoints

The primary objective of this program was to evaluate the efficacy of quetiapine versus placebo when used as adjunct with lithium or valproate in increasing time to recurrence of a mood episode. The time of recurrence of a mood event was defined as the time when the first of the following criteria was fulfilled:

Initiation of an antipsychotic, antidepressant, mood stabilizer other than the assigned mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a manic, depressed, or mixed event

The event of hospitalization for a manic or depressed or mixed event

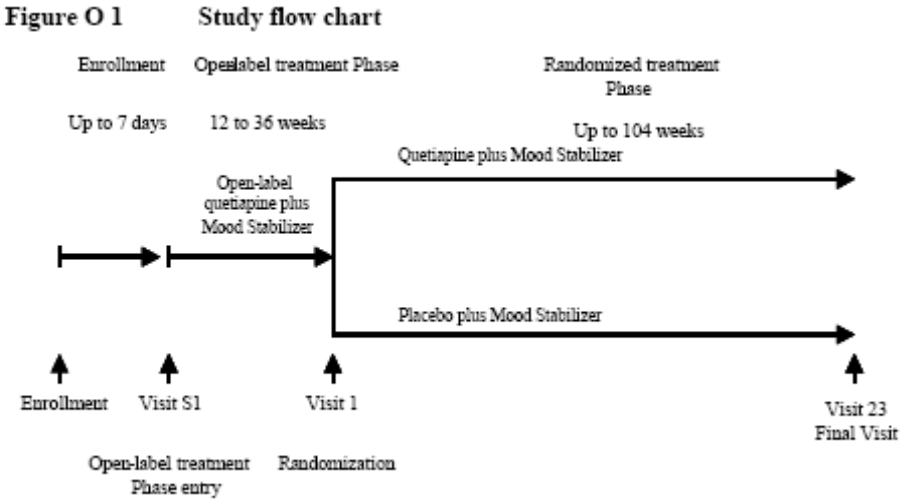
YMRS score ≥20 at 2 consecutive assessments or at the final assessment if the patient discontinues, or MADRS score ≥20 at 2 consecutive assessments or at the final

assessment if the patient discontinues

Discontinuation from the study by the patient if, in the opinion of the investigator, the discontinuation is due to a manic, depressed, or mixed event.

6.1.3 Study Design

Both studies consisted of an initial open-label treatment phase followed by a randomized treatment phase. See sponsor diagram below.



Patients enrolled in the 2 studies had a diagnosis of 1) Bipolar I Disorder, Most Recent Episode Manic (296.4x); 2) Bipolar I Disorder, Most Recent Episode Depressed (296.5x); or 3) Bipolar I Disorder, Most Recent Episode Mixed (296.6x), with or without psychotic features, as defined by Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition (DSM-IV). The 'most recent' episode could be current or occurring within 26 weeks of enrollment and treated with quetiapine and lithium or valproate.

Patients with bipolar II disorder were excluded in order to allow the assessment of recurrence of manic events.

Dosing during open-label treatment phase

The investigational product was administered twice daily.

Dosing with quetiapine was initiated at 100 mg/day on Day 1 and was increased to 400 mg/day on Day 4 in increments of 100 mg/day. The dose could then be increased to 600 mg/day on Day 5. The recommended target dosage of quetiapine was 600 mg/day, but the prescribed dosage could be adjusted within the range of 400 to 800 mg/day to maximize

efficacy and tolerability.

Dose regimen and dose adjustment for lithium or valproate were at the discretion of the investigator to achieve symptom control, to minimize side effects, and to achieve target trough serum concentrations of 0.5 mEq/L to 1.2 mEq/L for lithium and 50 ⌈g/ml to 125 ⌈g/ml for valproate during the entire length of the study.

Dosing during randomized treatment phase

Starting at the day of randomization, open-label 100-mg quetiapine tablets were replaced with 100-mg tablets of blinded investigational product at a rate of 1 tablet twice daily every 2 days. The rate of replacement could be slowed to increase tolerability. Replacement of open-label quetiapine with blinded investigational product had to be completed within 14 days (or 15 days for 800 mg/day). During this period the dose of blinded investigational product could be increased as clinically indicated to a maximum of 8 tablets/day (800 mg/day) (blinded and open-label medication combined). After all open-label tablets were replaced, the dose of blinded investigational product (quetiapine or placebo) was adjusted as clinically indicated within the dose range of 400 to 800 mg/day.

Key inclusion criteria for open-label treatment phase

For inclusion in the Open-label treatment Phase, patients had to fulfill all of the following criteria at enrollment;

1. A diagnosis of Bipolar I Disorder, Most Recent Episode Manic (296.4x), or Bipolar I Disorder, Most Recent Episode Depressed (296.5x), or Bipolar I Disorder, Most recent Episode Mixed (296.6x), with or without psychotic features, as defined by Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)

2. Male or female, at least 18 years old

3. At least 1 manic, depressed or mixed episode in the 2 years prior to the index episode (ie, the qualifying mood event as described in #1, above).

4. One of the following:

A current manic, depressed or mixed episode by DSM-IV criteria

A past manic, depressed or mixed episode within 26 weeks as documented by medical records, that was treated with quetiapine and mood stabilizer (lithium or valproate). Since this episode, treatment with this combination must not have been interrupted for more than 2 weeks continuously.

Key inclusion criteria for entering the randomized treatment phase

For inclusion in the randomized treatment phase, patients had to fulfill all of the following criteria during the open-label treatment phase:

1. Has been prescribed a dose of quetiapine within the range 400 to 800 mg/day and mood stabilizer (lithium or valproate) for at least 12 weeks

2. Young Mania Rating Scale (YMRS) ≤12 and Montgomery-Asberg Depression Rating Scale (MADRS) ≤12 assessed at a minimum of 4 consecutive visits spanning at least 12 weeks, with the allowance of a single excursion. An excursion was defined as a visit in which the YMRS or MADRS (or both) score equals 13 or 14. The excursion may not have occurred at the last of the consecutive visits

Timing of Introduction of Seroquel and Mood Stabilizer

The average time of stabilization before randomization was 15 weeks across both studies.

Both studies did not specify whether mood stabilizer or Seroquel would be started first. The sponsor's rational for this is given below in quotes.

"Approval is being sought for the use of quetiapine fumarate (SEROQUEL™, quetiapine) in the maintenance treatment of bipolar I disorder, as adjunct therapy to lithium or valproate. The therapeutic goal during the open-label stabilization period of these studies was concerned with stabilizing bipolar disorder in these patients as rapidly as clinically feasible on combination therapy. Restricting the order of introduction of the 2 treatments would have restricted the generalizability of the results in ways that may not be consistent with the variety of clinical settings in bipolar I disorder. Thus, the study protocols did not require a specific order of treatment initiation for quetiapine and the assigned mood stabilizer (lithium or valproate)."

See sponsor tables 3, 4, 5 and 6 below.

Table 3 **Timing of study medication initiation before or during open-label treatment (open-label safety population), based on 7-day window**

	Study 126 (N=1433) n (%)	Study 127 (N=1938) n (%)	126 + 127 (N=3371) n (%)
Patients started on MS > 7 days prior QTP(a)	412 (28.8)	355 (18.3)	767 (22.8)
Patients started on MS and QTP at approximately the same time(c)	557 (38.9)	1000 (51.6)	1557 (46.2)
Patients started on QTP > 7 days prior MS(b)	156 (10.9)	263 (13.6)	419 (12.4)
Other(missing dates, missing meds)	308 (21.5)	320 (16.5)	628 (18.6)

a Start date of assigned mood stabilizer > 7 days prior to start date of QTP
b Start date of QTP > 7 days prior to start date of assigned mood stabilizer
c Start date of assigned mood stabilizer within 7 days of QTP started
/cere/dev/seroquel/ctdmaintenance/sp/output/tlf/xa003.rtf xa221.sas 04FEB2008:14:34 luchen
MS mood stabilizer (lithium or placebo), QTP quetiapine. 126 D1447C00126. 127 D1447C00127.

Table 4 Timing of study medication initiation before or during open-label treatment (randomized safety population), based on 7-day window

	Study 126 (N=703) n (%)	Study 127 (N=623) n (%)	126 + 127 (N=1326) n (%)
Patients started on MS > 7 days prior QTP(a)	223 (31.7)	148 (23.8)	371 (28.0)
Patients started on MS and QTP at approximately the same time(c)	288 (41.0)	308 (49.4)	596 (44.9)
Patients started on QTP > 7 days prior MS(b)	78 (11.1)	95 (15.2)	173 (13.0)
Other(missing dates, missing meds)	114 (16.2)	72 (11.6)	186 (14.0)

a Start date of assigned mood stabilizer > 7 days prior to start date of QTP
b Start date of QTP > 7 days prior to start date of assigned mood stabilizer
c Start date of assigned mood stabilizer within 7 days of QTP started
/csre/dev/seroquel/ctdmaintenance/sp/output/tlf/xa004.rtf xa221.sas 04FEB2008:14:35 luchen
MS mood stabilizer (lithium or placebo). QTP quetiapine. 126 D1447C00126. 127 D144700127.

Table 5 Mean duration of stabilization for patients entering Randomisation Phase, by study and treatment (ITT population)

		126			127			126 + 127		
Duration		QTP N=336	PLA N=367	Total N=703	QTP N=310	PLA N=313	Total N=623	QTP N=646	PLA N=680	Total N=1326
Duration (weeks)	N	336	367	703	310	313	623	646	680	1326
	Mean (SE)	15.8(0.30)	16.4(0.31)	16.1(0.22)	13.9(0.33)	13.4(0.33)	13.7(0.23)	14.9(0.22)	15.0(0.24)	15.0(0.16)

ITT Intention -to-treat. MADRS Montgomery-Asberg Depression Rating Scale. N Number of patients in treatment group.
n Number of patients. QTP Quetiapine. SE Standard error. YMRS Young Mania Rating Scale.
The duration of stabilization is from the number of days (calculated retrospectively from the date of the first dose of Randomization) for which a patient's MADRS total score <=12 and YMRS total score <=12, with the allowance of a single excursion.
An excursion is defined as a visit in which the YMRS or MADRS (or both) score equals 13 or 14.
The excursion may not occur in the last visit before randomization.
/csre/dev/seroquel/ctdmaintenance/sp/output/tlf/xa005.rtf xa200.sas 07FEB2008:13:29 kscl497

Table 6 **[originally presented as Table SA 22 in Module 2.7.4] Disease characteristics (current) at enrollment (safety populations)**

		126+127 Open-label safety population (N=3371)	Randomized safety population (N=1326)
YMRS TOTAL SCORE AT ENROLLMENT	N [b]	3068	1326
	Mean(SD)	13.81(10.223)	12.45(10.296)
	Median	13.00	10.00
	Min to max	0 to 53	0 to 53
MADRS TOTAL SCORE AT ENROLLMENT	N [b]	3065	1326
	Mean(SD)	18.77(11.617)	15.10(11.530)
	Median	19.00	12.00
	Min to max	0 to 50	0 to 48
ASSIGNED MOOD STABILIZER N (%)		119 (3.5)	0
	Lithium	1346 (39.9)	561 (42.3)
	Valproate	1906 (56.5)	765 (57.7)
DSM-IV DIAGNOSIS OF BIPOLAR I DISORDER, MOST RECENT EPISODE N (%)	Manic	993 (29.5)	484 (36.5)
	Depressed	1139 (33.8)	397 (29.9)
	Mixed	1239 (36.8)	445 (33.6)
WITH RAPID CYCLING COURSE N [d] (%)	UNKNOWN	25 (0.7)	5 (0.4)
	NO	1881 (55.8)	835 (63.0)
	YES	1465 (43.5)	486 (36.7)

6.1.4 Efficacy Findings

Gerorge Koprdzakhis, Ph. D. had done the statistical review and concluded that the two studies are positive. See his comments below.

"In studies 126 and 127, quetiapine treatment arms (oral tablets 400mg to 800mg daily in divided doses) were statistically superior to corresponding placebo arms with respect to time to mood event when used as adjunct with a mood stabilizer (lithium or valproate). The p-values obtained from Cox-proportional hazard model were < 0.001. The sponsor wants to claim statistical significance of quetiapine on secondary endpoints: time to manic event and time to depressed event. However, the studies were not designed to collect time to first manic event and first depressed event separately. The primary efficacy endpoint (time to mood event) is a composite endpoint, defined as time to manic, depressed or mixed episode, whichever comes first. If a patient has a mood event due to a depressed episode, the time to first manic event would need to be censored on the date of the depressed episode and vice versa. Because of this issue, the results on these individual components as key secondary endpoints are difficult to interpret."

As shown in sponsor Table O 2, the results were quite similar across studies: In both studies, as well as in the pooled data analysis, quetiapine used as adjunct with lithium or valproate was superior to placebo used as adjunct with lithium or valproate in increasing time to recurrence of a mood episode. The risk of a mood event was reduced by 72% in Study 126 and by 68% in Study 127 in the quetiapine group as compared to the placebo group.

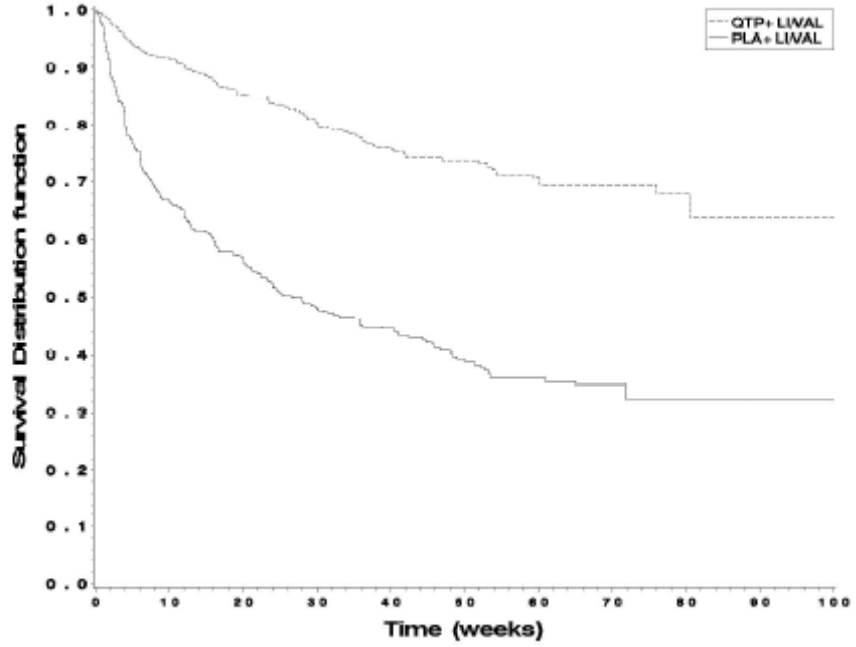
As shown in Figure O 2 for the combined studies, the mood event rate was lower in the quetiapine treatment group than in the placebo treatment group during the entire randomized treatment phase.

Sponsor Table O 2 Summary of mood event results (ITT population)

126	**127**	**126 + 127**
QTP + LI/VAL vs PLA + LI/VAL QTP N=336 / PLA N=367	**QTP + LI/VAL vs PLA + LI/VAL QTP N=310 / PLA N=313**	**QTP + LI/VAL vs PLA + LI/VAL QTP N=646 / PLA N=680**
Analysis of time to recurrence of a mood event		
95% CI 0.21, 0.37	0.24, 0.42	0.24, 0.37
Hazard ratio 0.28	0.32	0.30
p-value <.0001	<.0001	<.0001
Analysis of time to recurrence of a manic event		
95% CI 0.20, 0.44	0.18, 0.49	0.22, 0.41
Hazard ratio 0.30	0.30	0.30
p-value <.0001	<.0001	<.0001
Analysis of time to recurrence of a depressed event		
95% CI 0.17, 0.41	0.23, 0.48	0.23, 0.40
Hazard ratio 0.26	0.33	0.30
p-value <.0001	<.0001	<.0001

ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.
126 D1447C00126. 127 D1227C00127.
/csre/prod/seroquel/ctdmaintenance/sp/output/tlf/o2.rtf effy200.sas 28FEB2007:10:28 luchen

Figure O 2 **Time to recurrence of a mood event for the combined studies, Kaplan-Meier curves (ITT population)**



ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate.
Corresponds to Figure E 4, Module 2.7.3.

6.1.5 Clinical Microbiology

I have no comments.

6.1.6 Efficacy Conclusions

The sponsor, the statistical reviewer and I all agree that both studies are highly significant and support the indication of Seroquel for maintenance therapy as an adjunct to mood stabilizer. Studies 126 and 127 were statistically superior to placebo ($p < .001$) with respect to time to mood event when used as adjunct with a mood stabilizer (lithium or valproate).

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were 5 patients with serious AEs leading to death during or following the randomized treatment period, 2 of them occurring in the quetiapine treatment group and 3 in the placebo group.

There were 4 deaths during open-label treatment with quetiapine in combination with a mood stabilizer.

The deaths are similar to those currently in the label.

Patient narratives are provided in the individual Study 126 CSR and Study 127 CSR in patients who died, patients with SAEs, and patients who discontinued treatment because of AEs.

I have reviewed the narratives.

Table S 16 Listings of deaths during open-label treatment phase and randomized treatment phase

TREATMENT PERIOD AT AE ONSET	TREATMENT [a] / QTP DOSE [b]	CEN-TER	PATIENT NUMBER	SEX/ AGE[c] (YEARS)	TREATMENT DURATION OLT + RTP (DAYS)[d]	ADVERSE EVENT PREFERRED TERM/ INVESTIGATOR'S TEXT	TIME TO ONSET OF AE (DAYS)[e]	TIME TO DEATH (DAYS)[e]	CAUSAL-ITY[f]
OPEN-LABEL	QTP+LI /800mg	805	126-E0805016	Female/ 33	100 + 0	COMPLETED SUICIDE/ Suicide	101	101	No
	QTP+LI /800mg	805	126-E0805026	Male/ 64	8 + 0	PNEUMONIA/ Pneumonia	1	9	No
	QTP+VAL/400mg	1709	126-E1709025	Female/ 33	23 + 0	COMPLETED SUICIDE/ Suicide	113	113	No
	QTP+VAL/500mg	105	127-E0105001	Male/ 40	165 + 0	INJURY/ Severe trauma	165	165	No
RANDOM QTP	QTP+LI /400mg	1201	126-E1201014	Male/ 46	131 + 304	COMPLETED SUICIDE/ Suicide by self-hanging	329	329	No
	QTP+LI /600mg	48	127-E0048006	Female/ 41	196 + 55	COMPLETED SUICIDE/ Completed suicide	79	79	No
RANDOM PLA	PLA+LI /1600mg	202	126-E0202001	Male/ 55	259 + 42	DEATH/ Death-cause unknown	65	65	No
	PLA+LI /600mg	1006	126-E1006002	Female/ 50	82 + 167	CARDIAC FAILURE/ Heart failure	174	174	No
	PLA+VAL/400mg	303	126-E0303010	Male/ 38	168 + 22	COMPLETED SUICIDE/ Death by suicide	22	22	Yes

[a] Investigational product + mood stabilizer. [b] Dose (mg/day) at onset of AE leading to death.
[c] Age at enrollment. [d] From first dose to last dose of Investigational product.
[e] From first open-label dose to death in OLT and from first randomization dose to death in RTP.
[f] Causality to Investigational product, as assessed by the investigator.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. OLT Open-label treatment phase. RTP Randomized treatment phase.
Note: All deaths are included from start of open-label treatment phase up to 30 days following last dose of investigational product
Table corresponds to Table SA 47.

7.1.2 Other Serious Adverse Events

The proportion of patients with non-fatal SAEs ongoing at randomization or emerging during randomized treatment was 3.3% in the quetiapine group and 3.5% in the placebo group, and no major differences in SAEs between the randomized treatment groups were observed.

The non-fatal SAEs with more than 1 case in a treatment group was "depression" (2 cases in the quetiapine group) and "asthma" (2 cases in the placebo group). No differences were apparent between patients on the mood stabilizers lithium or valproate. These SAEs are similar to the current label.

Please see table in section 10.3.

I have reviewed the narratives for these events.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The tables below lists the reasons for drop out in the open-label and randomized phases and present no unusual findings.

Table S 6 Premature discontinuation from open-label treatment phase (open-label safety population)

	126 OLT QTP+ LI/VAL N=1433 n(%)	**127 OLT QTP+ LI/VAL N=1938 n(%)**	**126+127 OLT QTP+ LI/VAL N=3371 n(%)**
DISCONTINUED DURING OPEN-LABEL TREATMENT PHASE	728 (50.8)	1309 (67.5)	2037 (60.4)
ELIGIBILITY CRITERIA NOT FULFILLED	65 (4.5)	53 (2.7)	118 (3.5)
ADVERSE EVENT	210 (14.7)	398 (20.5)	608 (18.0)
LACK OF THERAPEUTIC RESPONSE	45 (3.1)	74 (3.8)	119 (3.5)
DEVELOPMENT OF STUDY DISCONTINUATION CRITERIA	0	0	0
PATIENT NOT WILLING TO CONTINUE	150 (10.5)	262 (13.5)	412 (12.2)
PATIENT LOST TO FOLLOW UP	107 (7.5)	329 (17.0)	436 (12.9)
TERMINATED BY SPONSOR	23 (1.6)	0	23 (0.7)
OTHER	128 (8.9)	193 (10.0)	321 (9.5)
COMPLETED OPEN-LABEL TREATMENT BUT NOT RANDOMIZED	1 (0.1)	1 (0.1)	2 (0.1)
ALL PATIENTS RANDOMIZED	704 (49.1)	628 (32.4)	1332 (39.5)

Table S 7 Premature discontinuation from randomized treatment phase (randomized safety population)

LI/VAL	126 + 127 QTP + N=646 n(%)	PLA + LI/VAL N=680 n(%)	TOTAL N=1326 n(%)
Premature discontinuation due to a mood event	125 (19.3)	343 (50.4)	468 (35.3)
Premature discontinuation due to other reason than mood event	198 (30.7)	137 (20.1)	335 (25.3)
Eligibility criteria not fulfilled	14 (2.2)	12 (1.8)	26 (2.0)
Adverse event	43 (6.7)	17 (2.5)	60 (4.5)
Lack of therapeutic response	2 (0.3)	1 (0.1)	3 (0.2)
Patient not willing to continue	58 (9.0)	42 (6.2)	100 (7.5)
Patient lost to follow up	35 (5.4)	31 (4.6)	66 (5.0)
Other	46 (7.1)	34 (5.0)	80 (6.0)
Completed randomized treatment phase a	323 (50.0)	200 (29.4)	523 (39.4)

7.1.3.2 Adverse events associated with dropouts

The total number of patients with AEs leading to discontinuation was 66 patients (5.0%) in the combined studies, with a higher incidence in the quetiapine group 6.7% compared to 3.4% in the placebo. "Weight increased" was the most common AE leading to discontinuation (12 patients in the quetiapine group [all reported in Study 127] and 2 patients in the placebo group), followed by "somnolence" (3 patients in the quetiapine group and 1 patient in the placebo group), "sedation" (3 patients in the quetiapine group and no patient in the placebo group), "alopecia" (2 patients in each treatment group), and "suicidal ideation" (2 patients in the quetiapine group and 1 patient in the placebo group).

In a summary of the AEs emerging during randomized treatment and leading to discontinuation, the percentage was 4.5% in the quetiapine group and 2.6% in the placebo group The most common AEs leading to discontinuation were "alopecia" (2 patients in the quetiapine group and 1 patient in the placebo group), "suicidal ideation" (2 patients in the quetiapine group and 1 patient in the placebo group, "insomnia" (3 patients in the placebo group), and "sleep disorder" (3 patients in the placebo group).

7.1.3.3 Other significant adverse events

I have no comments.

7.1.4 Other Search Strategies

AstraZeneca conducted an in-house review of suicidal behavior and ideation in the 2 studies in the quetiapine adjunct maintenance treatment program, following the process developed by the group at Columbia University under the leadership of Kelly Posner PhD. A group of AstraZeneca medical staff trained in psychiatry, but not associated with the 2 studies in this program, was identified to review the adverse events (AEs) for patients from Studies 126 and 127. These reviewers were trained in the Columbia review process and were apprised of the reconciliation process to be used in the event of discordant categorization of a particular patient with possible suicidal behavior by the 3 reviewers involved. All study data were blinded to the reviewers, except as provided in the narratives used for patient classification.

The sponsor reports that there is no indication of increased risk of suicidal behavior or ideation with the administration of quetiapine at doses of 400 mg to 800 mg daily, compared with the administration of placebo, when used in the maintenance treatment of bipolar I disorder in combination with lithium or valproate.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were elicited regularly through out these studies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

MedDRA terms were used by the sponsor and appear to be appropriate.

7.1.5.3 Incidence of common adverse events

The most common AEs by preferred term emerging after randomization in the quetiapine treatment group were “headache” (7.4% of patients in the quetiapine group and 9.3% in the placebo group), “nasopharyngitis” (7.1% in the quetiapine group and 7.2% in the placebo group), and “upper respiratory tract infection” (6.7% in the quetiapine group and 4.0% in the placebo group). Events of “insomnia” were reported in 6.5% of patients in the quetiapine group and 16.6% in the placebo group. When the AEs ongoing at randomization (ie, starting during open-label treatment and continuing into the randomized phase) were added to those emerging after randomization, the most common AEs (≥5%) reported in the quetiapine treatment group were “weight increased” (20.1% of patients in the quetiapine group and 14.4% of the patients in the placebo group), “sedation” (11.6% in the quetiapine group and 10.0% in the placebo group), “somnolence” (10.7% in the quetiapine group and 8.5% in the placebo group), and “dry mouth” (10.7% in the quetiapine group and 9.6% in the placebo group). The most common non-fatal SAE was “suicidal ideation”, with 3 patients in each

treatment group. The only other non-fatal SAEs with more than 1 case in a treatment group were "depression" (2 cases in the quetiapine group) and "asthma" (2 cases in the placebo group)

7.1.5.4 Common adverse event tables

Table S 15 Common adverse events (randomized safety population)

	126+127 Randomized treatment		Assigned mood stabilizer			
	QTP+LI/VAL (N=646)	PLA+LI/VAL (N=680)	QTP+LI (N=274)	PLA+LI (N=287)	QTP+VAL (N=372)	PLA+VAL (N=393)
MEDDRA PREFERRED TERM[a]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ANY ADVERSE EVENT	185 (28.6)	261 (38.4)	89 (32.5)	127 (44.3)	96 (25.8)	134 (34.1)
HEADACHE	48 (7.4)	63 (9.3)	25 (9.1)	30 (10.5)	23 (6.2)	33 (8.4)
NASOPHARYNGITIS	46 (7.1)	49 (7.2)	18 (6.6)	21 (7.3)	28 (7.5)	28 (7.1)
UPPER RESPIRATORY TRACT INFECTION	43 (6.7)	27 (4.0)	21 (7.7)	14 (4.9)	22 (5.9)	13 (3.3)
INSOMNIA	42 (6.5)	113 (16.6)	22 (8.0)	56 (19.5)	20 (5.4)	57 (14.5)
TREMOR	39 (6.0)	34 (5.0)	14 (5.1)	18 (6.3)	25 (6.7)	16 (4.1)
NAUSEA	38 (5.9)	52 (7.6)	24 (8.8)	34 (11.8)	14 (3.8)	18 (4.6)
DIARRHOEA	19 (2.9)	41 (6.0)	9 (3.3)	23 (8.0)	10 (2.7)	18 (4.6)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. n Number of patients. MedDRA Medical Dictionary of Regulatory Activities.
126 D1447C00126. 127 D144700127.
Note: Common adverse event: Adverse events occurring at an incidence of >= 5% in any randomized treatment group. Events emerging during randomized treatment phase by decreasing frequency in the QTP+LI/VAL group.

7.1.5.5 Identifying common and drug-related adverse events

The current US label lists AEs "associated with the use of SEROQUEL"; ie, those that occurred in placebo-controlled trials with an incidence in quetiapine-treated patients that was at least 5% and at least twice that observed in placebo-treated patients. No events emerging during the randomized treatment phase of the current program met these criteria for "association" with quetiapine. Two AEs had an incidence in the randomized quetiapine treatment group that was at least 5% and higher (but not twice as high) as the incidence in the placebo group: upper respiratory tract infection (6.7% vs 4.0%) and tremor (6.0% vs 5.0%). The other AEs with an incidence of at least 5% in the quetiapine group were headache (7.4%), nasopharyngitis (7.1%), insomnia (6.5%), and nausea (5.9%), all of which had a higher incidence in the placebo group.

7.1.5.6 Additional analyses and explorations

I have no comments.

7.1.6 Less Common Adverse Events

I have no comments.

7.1.7 Laboratory Findings

As the safety profile of Seroquel is well known I will use this section simply to highlight sponsor findings of interests in this submission which I have veriflied.

Hematology:

Shifts to neutrophil values <1.5 x 10^9/L at any time during randomized treatment were observed in 10 patients (1.7%) in the quetiapine group compared to 4 patients (0.7%) in the placebo group. All of the patients with a neutrophil value <1.5 x 10^9/L in both groups were on combination treatment with valproate. Three patients in the quetiapine group and 2 patients in the placebo group with treatment emergent shifts to neutrophils <1.5 x 10^9/L had this value present at the end of treatment.

One patient in each group had a treatment emergent neutrophil value <1.0 x 10^9/L during randomized treatment. The 2 patients (E0020051 and E0059017 in Study 127) had AEs with preferred MedDRA terms "neutropenia" and "laboratory abnormalities", respectively, reported. Both patients were discontinued from treatment due to the AE.

No case of a neutrophil value <0.5 x 10^9/L was observed in any study during randomized treatment. There were 18 patients (3.1%) in the quetiapine group and 15 patients (2.5%) in the placebo group with treatment emergent high neutrophils (≥10.0 x 10^9/L), a majority of them (14 and 9 patients, respectively) on combination treatment with lithium.

Hepatic:

The change from randomization to end of treatment in hepatic laboratory data was small in the combined studies as well as in separate studies.

Mean AST and ALT increased slightly in the quetiapine treatment group (0.63 U/L and 1.46 U/L, respectively) and alkaline phosphatase was stable, compared to small decreases for all 3 variables in the placebo group (-0.36 U/L, -0.98 U/L, and –3.84 U/L, respectively). However, there were no changes in medians from randomization to end of treatment in the quetiapine group in any of the hepatic laboratory variables.

At end of treatment, 3 patients in the quetiapine group had a high AST, 2 patients had a high ALT, and 1 patient had a high total bilirubin. In the placebo group, 2 patients had a high AST, 4 patients had a high ALT, and 1 patient had a high total bilirubin.

Renal:

13 clinically important renal laboratory values were reported. Seven patients in the quetiapine group compared to 1 patient in the placebo group were reported to have a treatment-emergent increased creatinine value during randomized treatment. The incidence of treatment-emergent elevated BUN values was 3 patients in the quetiapine group and 2 patients in the placebo group.

Electrolyte:

There were small decreases from randomization to end of treatment in electrolyte laboratory data in both treatment groups, and no major differences between treatment groups were observed.

Glucose:

Treatment-emergent clinically important (as defined by AstraZeneca: any blood glucose ≥126 mg/dL: any blood glucose ≥200 mg/dL: any HbA1c >7.5%) glucose regulation laboratory values at any time during randomized treatment were more common in the quetiapine group compared to the placebo group. There were treatment emergent shifts to glucose values ≥126 mg/dL in 68 patients (12.2%) in the quetiapine group, compared with 47 patients (8.1%) in the placebo group. Treatment emergent glucose values ≥200 mg/dL at any time during randomized treatment were reported in 17 patients (2.9%) in the quetiapine group and in 3 patients (0.5%) in the placebo group. HbA1c values were elevated (>7.5%) in 12 patients (2.1%) in the quetiapine group, compared with 5 patients (0.8%) in the placebo group.

Lipid:

Changes in lipid laboratory data were small from randomization to end of treatment. Total cholesterol, LDL, and triglyceride values were stable in the quetiapine group, and each improved somewhat in the placebo group. HDL levels changed very little in either the quetiapine or placebo treatment groups.

Thyroid:

The changes from randomization to end of treatment in thyroid laboratory data were small. There was a mean increase in TSH of 0.38 μU/mL in the quetiapine group compared to a decrease in the placebo group of -0.59 μU/mL. The variability in the quetiapine group was relatively large, and the median change was a decrease of -0.09 μU/mL in the quetiapine group compared to –0.26 μU/mL in the placebo group. Free T4 and T3 levels were stable in

both quetiapine and placebo treatment groups.

Prolactin:

The change from randomization to end of treatment in prolactin laboratory data was small and similar between treatment groups.

Vital signs:

The mean changes in vital sign data from randomization to end of treatment were small and generally consistent with current knowledge about quetiapine treatment.

EKG

There were no apparent differences observed in ECG data between the randomized treatment groups, besides slightly more patients having clinically important heart rate increases in the quetiapine treatment group (9.9%) compared to the placebo group (5.6%).

Quetiapine was not associated with QT and QT_c changes.

EPS

There were no major differences between the randomized treatment groups either with respect to the number of reports of AEs potentially associated with EPS; changes in the SAS, BARS, and AIMS rating scores ; or use of anticholinergics, a surrogate marker for EPS.

WEIGHT

The mean weight change during randomized treatment was 0.5 kg in the quetiapine group and –1.9 kg in the placebo group. Weight increases of ≥7% were more common in the quetiapine group than in the placebo group (9.3% vs 2.7%), whereas weight decreases of ≥7% were less common (6.9% vs 14.6%). The mean change from enrollment to the end of randomized treatment was 4.8 kg in the quetiapine group. Aggregated assessment of AEs potentially associated with diabetes mellitus indicated a higher incidence in the quetiapine treatment group (3.1%) compared with the placebo treatment group (1.0%); however, most of the terms are not specific for a diagnosis of diabetes mellitus. In addition, changes in glucose regulation laboratory data were observed in the quetiapine treatment group, including an increased incidence of hyperglycemia: the proportion of patients who had an increased blood glucose level ≥126 mg/dL was 12.2% for quetiapine and 8.1% for placebo. Adjusting for the longer duration of exposure in the quetiapine group, the rates were 21.6 per 100 patient years for quetiapine and 18.9 per 100 patient years for placebo.

7.1.7.5 Special assessments

The incidence of common AEs in patients with bipolar I disorder who received quetiapine as adjunct with lithium or valproate was generally consistent across mood stabilizer, age, sex, and race. Note that no patients younger than 18 years and few patients older than 65 years (11 patients in the quetiapine group and 15 in the placebo group) were included in the studies.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program

Study 126 was mainly conducted outside of the United States. ECG tracings are included in the patients' Case Report Forms for this study as part of local marketing company requirements. ECG tracings are not provided for study 127 which was conducted in the United States.

7.1.10 Immunogenicity

I have no comments.

7.1.11 Human Carcinogenicity

I have no comments.

7.1.12 Special Safety Studies

I have no comments.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There were no reports of drug abuse or withdrawal symptoms.

7.1.14 Human Reproduction and Pregnancy Data

There were 7 pregnancies reported in Study 126 and 14 pregnancies reported in Study 127. There were no unusual reports involving these pregnancies.

7.1.15 Assessment of Effect on Growth

I have no comments.

7.1.16 Overdose Experience

Both studies had several overdoses and one patient died folowing an overdose.

7.1.17 Postmarketing Experience

The application for quetiapine in maintenance treatment of bipolar I disorder as combination therapy to lithium or valproate is first being submitted in the United States (2Q07).

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

This safety program was suitable to assess the safety of quetiapine in maintenance treatment of bipolar I disorder. The number of patients providing safety data in the program and the total exposure in patient-years were 1326 patients in the randomized safety population, 3371 patients in the open-label safety population.

7.2.1.2 Demographics

The open-label safety population and the randomized safety population were similar with respect to demographic characteristics at enrollment. The mean age was approximately 40 years; 1.6% of patients were >65 years in the open-label safety population. Both sexes were evenly represented; there were 44% males in the open-label safety population. The open-label safety population was predominantly Caucasian (85.6%), with 9.4% Blacks.

In the randomized safety population, the quetiapine and placebo treatment groups in Study 126 and Study 127 and in the combined studies were well-matched with respect to demographic characteristics. Mean age was 41.2 years overall, and was consistent across studies and treatment groups, although the distribution in different age groups differed slightly. The quetiapine treatment group compared to placebo had a lower proportion of patients in the age 18 to 39 years (42.4% vs 48.1%) and a corresponding higher proportion of patients 40 to 65 years of age (55.9% vs 49.7%). In the combined studies, there were 26 elderly (>65 years) patients (2.0%), 11 patients (1.7%) in the quetiapine group and 15 patients (2.2%) in the placebo group). The mean weight was approximately 2 kg greater at

randomization in the pooled quetiapine group (89.2 kg) compared to the placebo group (87.1 kg). Mean weight was greater in Study 127 (92.7 kg) compared to Study 126 (84.1 kg). The percentage of patients in BMI category 30 to <40 kg/m2 was greater in Study 127 (45.7%) compared to Study 126 (31.7%). There were no major imbalances between Study 126 and Study 127 that precluded pooling of data.

Manic or mixed episodes in the year prior to enrollment were more prevalent in Study 127 (overall mean 4.0, median 2.0) compared to Study 126 (overall mean 2.5, median 1.0).

There was some variation across studies in total bipolar episodes in the year prior to enrollment. In Study 126, the overall mean was 5.0, median 2.0 and was nearly the same in the quetiapine and placebo treatment groups. In Study 127, the overall mean was 7.3, median 4.0, and the mean number was higher (7.9, median 3.0) in the quetiapine group compared to placebo (mean 6.6, median 4.0).

In the randomized safety population, mean age at first bipolar episode was 24.6 years. Mean duration since first known bipolar episode was 17.0 years. For these characteristics, there was similarity across studies and between treatment groups.

7.2.1.3 Extent of exposure (dose/duration)

Conclusions on quetiapine dosing in open-label treatment phase and during randomized treatment phase

The full quetiapine dose range of 400 to 800 mg/day was used in both Study 126 and Study 127. The most common median quetiapine dose at randomization (last dose in open-label treatment) and during the randomized treatment phase was 400 mg/day. The mean dose of quetiapine at randomization (last dose in open-label treatment) was 492 mg/day; mean dose during the randomized treatment phase was 507 mg/day.

Derivation of open-label safety population

	126 + 127 OLT QTP+ LI/VAL n(%)
All patients enrolled a	3414 (100.0)
Excluded from open-label safety population b	43 (1.3)
Open-label safety population	3371 (98.7)

In total, 3414 patients were enrolled in the open-label phase in the combined studies. Few enrolled patients (43, [1.3%]) were excluded from the open-label safety population, 28 of them in Study 126 and 15 in Study 127. The reason for exclusion was that the patients did not

receive any dose of the study drug.

Sponsor Table S 8 Total exposure to quetiapine or placebo in patient years by assigned mood stabilizer during randomized phase (randomized safety population)

126 QTP+LI/VAL N = 336		**PLA+LI/VAL N = 367**	**127 QTP+LI/VAL N = 310**	**PLA+LI/VAL N = 313**	**126 + 127 QTP+LI/VAL N = 646**	**PLA+LI/VAL N = 680**
Lithium						
Valproate	76.59 96.24	50.86 79.58	89.50 113.14	64.19 87.10	166.09 209.37	115.05 166.68
Total	172.83	130.44	202.64	151.29	375.47	281.73

The mean duration of exposure to quetiapine was 213 days during the randomized treatment phase. The mean duration of exposure to placebo was 152 days.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There are no other studies.

7.2.2.2 Postmarketing experience

There is no postmarkering experience for this indication.

7.2.2.3 Literature

See 8.6

7.2.3 Adequacy of Overall Clinical Experience

The clinical experience by agreement with the FDA is adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

N/A

7.2.5 Adequacy of Routine Clinical Testing

The clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

N/A

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This section was adequate.

7.2.8 Assessment of Quality and Completeness of Data

This section was adequate.

7.2.9 Additional Submissions, Including Safety Update

There were no safety updates or addition submissions.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

N/A

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

These studies were similar and data was pooled.

7.4.1.1 Pooled data vs. individual study data

The individual data and pooled data is similar for efficacy and safety.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

There was no evidence of dose dependency in these two studies.

7.4.2.2 Explorations for time dependency for adverse findings

There was no evidence of time dependency in these two studies.

7.4.2.3 Explorations for drug-demographic interactions

In the quetiapine group, a higher incidence of "insomnia" was reported by patients in the "Black" category compared with "Caucasian" patients (16.7% and 5.6%, respectively), otherwise incidences were similar across the 2 ethnic categories. In patients randomized to placebo, higher incidences of "headache", "nasopharyngitis", and "nausea" were reported by patients in the "Black" category compared with "Caucasian" patients.

7.4.2.4 Explorations for drug-disease interactions

There were no new significant findings.

7.4.2.5 Explorations for drug-drug interactions

See section 8.2.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

These two studies did not specify whether Seroquel or mood stabilizer should be started first. 400-800 mg of Seroquel was used.

8.2 Drug-Drug Interactions

The absence of a clinically relevant pharmacokinetic interaction between quetiapine and lithium and between quetiapine and valproate is already noted in the current prescribing information for quetiapine.

8.3 Special Populations

The incidence of common AEs in patients with bipolar I disorder who received quetiapine as adjunct with lithium or valproate was generally consistent across mood stabilizer, age, sex, and race. Note that no patients younger than 18 years and few patients older than 65 years (11 patients in the quetiapine group and 15 in the placebo group) were included in the studies.

8.4 Pediatrics

As stated in the 12 January 2007 pre-sNDA FDA Responses, a partial pediatric waiver for pediatric patients <12 years of age and a deferral of pediatric studies for adolescents 12 to 16 years of age was granted.

8.5 Advisory Committee Meeting

I do not believe an advisory committee is needed.

8.6 Literature Review

All relevant safety issues from the periodic safety update report (PSUR) covering the report period of 1 August 2005 - 31 July 2006 were taken into consideration by the sponsor's Drug Safety department for this supplement. The literature from 01 August 2005 through 31 July 2006 for SEROQUEL was reviewed utilizing Planet (an internal AstraZeneca database for indexing biomedical literature, which searches over 14,000 journals daily), BIOSYS Previews, EMBASE, IPAB, PsycINFO, Ovid MEDLINE(R). The search was designed to capture all relevant safety information with the use of the active ingredient, quetiapine.

Following, a comprehensive review of the AE reports in the PSUR line listing, and the scientific/medical literature received during the reporting period, no new significant safety issues bearing on the established overall safety profile of SEROQUEL were identified by the sponsor.

8.7 Postmarketing Risk Management Plan

I have no recommendations.

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

These two studies are supportive for this indication and the FDA statistical reviewer, Gerorge Koprdzakhis, Ph. D agrees.

The safety results in this program show that quetiapine is reasonable safe when used as adjunct with lithium or valproate in long-term treatment. The safety profile was generally similar to the

current safety and tolerability profile of quetiapine in the acute treatment of schizophrenia, mania, and bipolar depression, as described in the current US prescribing information.

9.2 Recommendation on Regulatory Action

I recommend that we approve Seroquel for maintenance treatment of bipolar I disorder, as adjunct therapy to lithium or valproate.

9.3 Recommendation on Postmarketing Actions

I have no recommendations.

9.3.1 Risk Management Activity

I have no recommendations.

9.3.2 Required Phase 4 Commitments

I have no recommendations.

9.3.3 Other Phase 4 Requests

I have no recommendations.

9.4 Labeling Review

I have reproduced the key labeling changes below. They seem acceptable with two possible exceptions The label needs a clarifying statement regarding the timing of the introduction of Seroquel and mood stabilizer dosing. The study descriptions should state the average time of stabilization before randomization (15 weeks) and should not celebrate the number of weeks of post randomization improvement.

1 INDICATIONS AND USAGE

1.1 Bipolar Disorder

SEROQUEL is indicated for the treatment of ~~both~~:

- depressive episodes associated with bipolar disorder
- acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex.
- maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex.[1]

[1]Module 2, Clinical Summary of Efficacy, 2.7.3.2, Table E-3

Mania

The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania [*see Clinical Pharmacology (12)*]. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy. (b) (4)

(b) (4) deleted as long term data is now available.

~~The physician who elects to use SEROQUEL for extended periods in bipolar disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).~~

Paragraph was moved to Maintenance Treatment

Maintenance Treatment

The efficacy of SEROQUEL (administered twice daily totalling 400 to 800 mg per day), as adjunct maintenance therapy to lithium or divalproex, was established in 2 identical randomized placebo-controlled double-blind studies that included patients with bipolar I disorder treated up to 104 weeks.[2] [*see Clinical Studies (14)*]

[2] Module 2, Clinical Summary of Efficacy, 2.7.3.2, Table E-3

The physician who elects to use SEROQUEL for extended periods in bipolar disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient [*see Dosage and Administration (2)*].

Doage and ADmisistration

Maintenance

(b) (4)

(b) (4)

Maintenance of efficacy in bipolar I disorder was demonstrated with SEROQUEL (administered twice daily totalling 400 to 800 mg per day) as adjunct therapy to lithium or divalproex. [*see Clinical Studies (14)*].[4]

[4] Module 2, Clinical Summary of Efficacy, 2.7.3.2

6 ADVERSE REACTIONS

6.1 Clinical Study Experience

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

The information below is derived from a clinical trial database for SEROQUEL consisting of over (b) (4) 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.

[4,5] Module 2, Summary of Clinical Safety, 2.7.4.1.2.1

Of these approximately (b) (4) 4300 subjects, approximately (b) (4) 4000 (2300 in schizophrenia, 405 in acute bipolar mania, ~~and~~ 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 (b) (4) 2400[4,5] patient-years.

Bipolar Maintenance

The two long-term placebo-controlled trials for the maintenance treatment of bipolar I disorder included patients (n=1326) whose most recent episode was manic, depressed, or mixed. Patients were required to be stable on SEROQUEL plus lithium or divalproex for 12 weeks during the open-label phase prior to randomization. Patients were randomized to receive either SEROQUEL (administered twice daily totalling

[5] Module 2, Summary of Clinical Safety, 2.7.4.2 and Table SA 34

400 to 800 mg per day) or placebo as adjunct therapy to lithium or divalproex for up to 104 weeks. Table 5 contains the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during the randomization period in long term therapy of bipolar maintenance (up to 104 weeks) in 3% of patients where the incidence in patients in the SEROQUEL treatment group was greater than the incidence in the placebo treated group.[5] patients.

Table 5: Treatment-Emergent Adverse Experience Incidence in Long-Term Therapy of Bipolar Maintenance (up to 104 weeks) in 3% or more patients (Adjunct Therapy)

	SEROQUEL (n=646)	Placebo (n=680)
Nervous System Disorders		
Tremor	6%	5%
Somnolence	5%	2%
Sedation	4%	2%
Infections and Infestations		
Upper respiratory tract infection	7%	4%
Gastrointestinal Disorders		
Constipation	3%	2%
Musculoskeletal and Connective Tissue Disorders		
Back pain	5%	4%
Arthalgia	4%	3%
Psychiatric Disorders		
Anxiety	3%	2%
General Disorders and Administration Site Conditions		
Fatigue	3%	2%
Respiratory, Thoracic and Mediastinal Disorders		
Cough	4%	2%
Pharyngolaryngeal pain	3%	1%
Investigations		
Weight increased	5%	4%
Endocrine Disorders		
Hypothyroidism	4%	1%

[1]Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: headache, nasopharyngitis, insomnia, nausea, influenza, vomiting, diarrhea, and toothache.

In two long-term studies in bipolar maintenance, following an open-label stabilization phase, the incidence of adverse events potentially related to EPS from randomization to end of treatment for the combined data was similar SEROQUEL (7.9%) and placebo (6.9%). The use of anticholinergic medications was also similar across treatment groups.[6]

Clincial Studies

The majority of patients in this trial taking SEROQUEL were dosed in a range between 400 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.

[7] Module 2, Clinical Summary of Efficacy, 2.7.3.3.1.2, Table E-8

Maintenance Therapy

The efficacy of SEROQUEL in the maintenance treatment of bipolar I disorder was established in 2 placebo-controlled trials in patients (n=1326)[7] 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 12 weeks in order to be randomized. In the randomization phase, patients continued treatment with lithium or divalproex and were randomized to receive either SEROQUEL (administered twice daily totalling 400 to 800 mg per day) or placebo for up to 104 weeks.[8] 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, hospitalization, YMRS score ≥ 20 or MADRS score ≥ 20 at 2 consecutive assessments, or study discontinuation due to a mood event. Secondary variables included time to a manic event and time to a depressed event.[9]

[8] Module 2, Clinical Summary of Efficacy, 2.7.3.2, Table E-2

[9] Module 2, Clinical Summary of Efficacy, 2.7.3.1.3.8

In both studies, SEROQUEL was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed episode). The risk of recurrence of a mood event was reduced by 70% in patients treated with SEROQUEL ($p<.0001$, HR 0.30).[10] SEROQUEL was also superior to placebo for increasing the time to a manic event and time to a depressed event.[11] Efficacy was demonstrated to be independent of most recent episode (manic, mixed, or depressed) and adjunct mood stabilizer (lithium or divalproex).[12]

[10] Module 2, Clinical Summary of Efficacy, 2.7.3.3.2.1.1

[11] Module 2, Clinical Summary of Efficacy, 2.7.3.3.2.3.1 and 2.7.3.3.2.4.1

[12] Module 2, Clinical Summary of Efficacy, 2.7.3.3

9.5 Comments to Applicant

I have no additional comments.

10 APPENDICES

10.1 Review of Individual Study Reports

Study D1447C00126 (Sponsor Summary)

A Multicenter, Randomized, Parallel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (Oral Tablets 400 mg to 800 mg Daily in Divided Doses) to Placebo when Used as Adjunct to a Mood Stabilizer (Lithium or Valproate) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients

This study was conducted in 177 centers in 18 countries.

The primary objective was to evaluate the efficacy of quetiapine versus placebo when used as adjunct to mood stabilizer (lithium or valproate) in increasing time to recurrence of a mood event.

Recurrence was defined as (1) initiation of an antipsychotic, antidepressant, mood stabilizer other than the assigned mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a manic, depressed or mixed event, (2) hospitalization for a manic, depressed or mixed event, (3) Young Mania Rating Scale (YMRS) (Young et al 1978) score ≥20 at 2 consecutive assessments or at the final assessment if the patient discontinues, or Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) score ≥20 at 2 consecutive assessments or at the final assessment if the patient discontinues, or (4) discontinuation from the study by the patient if, in the opinion of the investigator, the discontinuation was due to a manic, depressed or mixed event.

Study design

This was a multicenter, randomized, parallel-group, double-blind study to compare quetiapine with placebo when used as adjunct to lithium or valproate in the maintenance treatment of adult patients with bipolar I disorder for up to 104 weeks. The study consisted of enrollment and 2 phases, the initial open-label treatment phase and the subsequent randomized treatment phase. To be eligible for randomization, a patient must have been treated with quetiapine within the range of 400 to 800 mg/day and mood stabilizer (lithium or valproate) for at least 12 weeks during the open-label treatment phase. To be randomized, a patient also had to have a YMRS total score ≤12, and a MADRS total score ≤12 assessed at a minimum of 4 consecutive visits spanning at least 12 weeks, with the allowance of a single excursion with a YMRS and/or MADRS total score of 13 or 14 (unless this occurred on the last of the

4 consecutive visits).

Patients began or continued on an oral dose of open-label quetiapine, 400 to 800 mg daily in divided doses, with a recommended target dose of 600 mg/day, after meeting all inclusion and none of the exclusion criteria for entering the open-label treatment phase. Doses could be adjusted within this range to maximize efficacy and tolerability. After meeting all inclusion criteria and none of the exclusion criteria for randomization, patients were randomized either to quetiapine or placebo twice daily. After randomization, open-label 100-mg quetiapine tablets (from a specific visit pack for this phase) were titrated down and replaced with 100-mg tablets of blinded investigational product (provided by the investigator or a designee) at a rate of 1 tablet per every 2 days. The dose of blinded investigational product (quetiapine or placebo) could be adjusted as clinically indicated within the dose range of 400 to 800 mg/day all through the randomized treatment phase.

Duration of treatment
The study consisted of enrollment and 2 phases: open-label treatment phase (12 weeks to 36 weeks), and randomized treatment phase (up to 104 weeks).

RESULTS:

In patients with bipolar I disorder, quetiapine as adjunct with a mood stabilizer (lithium or valproate) significantly increased the time to recurrence of a mood event (manic or depressed) compared to placebo adjunct with a mood stabilizer (estimated hazard ratio 0.28, corresponding to a risk reduction of 72%). Kaplan-Meier estimates of time to 20% of the patients experiencing recurrence of a mood event was 211 days for the quetiapine treatment group and 30 days in the placebo treatment group. The demonstrated efficacy of quetiapine did not show restriction to any specific subgroup (assigned mood stabilizer, age, sex, race, index episode, or precence of rapid cycling) and the results in the primary ITT population were supported by the results in the PP population. Likewise, quetiapine significantly increased the time to recurrence of a manic episode (estimated hazard ratio 0.30, corresponding to a risk reduction of 70%) and a depressed episode (estimated hazard ratio 0.26, corresponding to a risk reduction of 74%), respectively, compared to placebo. The time to all-cause discontinuation from the study was greater in the quetiapine treatment group.

Sponsor Table S 2 **Efficacy results, time to event, randomized treatment phase (ITT population)**

QTP + LI/VAL vs PLA + LI/VAL QTP N=336 / PLA N=367

Analysis of time to recurrence of a mood event	
Hazard ratio	0.28
95% CI	0.21, 0.37
p-value	<.0001
Analysis of time to recurrence of a manic event	
Hazard ratio	0.30
95% CI	0.20, 0.44
p-value	<.0001
Analysis of time to recurrence of a depressed event	
Hazard ratio	0.26
95% CI	0.17, 0.41
p-value	<.0001

ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.
/csre/dev/seroquel/d1447c00126/sp/output/tlf/t11020101.rtf mood201.sas 10JAN2007:14:50 kwcn867

Sponsor Table S 3 Summary of efficacy results between mood events, LS means and treatment comparisons of rating scales (ITT population)

Outcome variable	LS mean (SE)		Difference in LS means (SE)	95% CI	P-value
	QTP + LI/VAL (N =)	PLA + LI/VAL (N =)			
SDS total score, mean changea	-0.55 (0.302)	0.13 (0.312)	-0.68 (0.432)	-1.53, 0.17	0.1149
Additional rating scalesb					
PGWB total score	102.46 (0.601))	100.54 (0.697)	1.92 (0.834)	0.28, 3.55	0.0218
YMRS total score	2.44 (0.093)	3.34 (0.148)	-0.90 (0.161)	-1.21, -0.58	<0.0001
MADRS total score	3.55 (0.129)	4.28 (0.154)	-0.73 (0.175)	-1.07, -0.39	<0.0001
CGI-BP Severity of Illness	1.53 (0.022)	1.67 (0.028)	-0.14 (0.031)	-0.20, -0.08	<0.0001
CGI-BP Global Improvement	3.91 (0.039)	4.08 (0.045)	-0.18 (0.051)	-0.28, 0.08	0.0006
PANSS-P score	7.68 (0.049)	7.90 (0-054)	-0.22 (0.063)	-0.35, -0.10	0.0005

Narrative of results for Study D1447C00126
Patient population

There were 1461 patients enrolled into the study, 1433 received open-label treatment with quetiapine, and thus were included in the open-label safety population. Of the 1461 enrolled patients, 706 patients were randomized to treatment with quetiapine or placebo used as adjunct to a mood stabilizer (lithium or valproate), 3 of whom did not receive any randomized study medication, so 703 patients were included in the randomized safety population (336 receiving quetiapine and 367 receiving placebo). Of those, all 703 were included in the ITT population, the primary population for analyses of efficacy results.

The 2 treatment groups were well matched as to demographic and baseline disease characteristics. Patients had an overall mean age of approximately 42 years, and 53% were female. The YMRS total score and MADRS total score at randomization were similar in the 2 treatment groups. At randomization, more patients (48.5%) had a manic episode as the most recent bipolar episode, compared to 28.9% with a depressive episode, and 22.6% with a mixed episode.

Due to the efficacy of quetiapine at preventing or delaying mood events, the mean exposure during the randomized period was approximately 44% longer to quetiapine than to placebo (189 and 130 days respectively).

Study: D1447C00127 (Sponsor Summary)

A Multicenter, Randomized, Parallel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (Oral Tablets 400 mg to 800 mg Daily in Divided Doses) to Placebo when Used as Adjunct to a Mood Stabilizer (Lithium or Valproate) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients

Study centre(s)

This study was conducted in 127 centers in the United States and Canada.

This was a multicenter, randomized, parallel-group, double-blind study to compare quetiapine with placebo when used as adjunct to lithium or valproate in the maintenance treatment of adult patients with Bipolar I Disorder (both mania and depression) for up to 104 weeks. The study consisted of enrollment and 2 phases, the initial open-label treatment phase and the

subsequent randomized treatment phase. To be eligible for randomization, a patient must have been treated with quetiapine within the range of 400 to 800 mg/day and mood stabilizer (lithium or valproate) for at least 12 weeks during the open-label treatment phase. To be randomized, a patient also had to have a YMRS total score ≤12, and a MADRS total score ≤12 assessed at a minimum of 4 consecutive visits spanning at least 12 weeks, with the allowance of a single excursion with a YMRS and/or MADRS score of 13 or 14 (unless this occurred on the last of the 4 consecutive visits).

Male or female patients, aged 18 years or older, with Bipolar I Disorder, who had experienced an acute manic, depressed or mixed episode at enrollment; or a past manic, depressed or mixed episode within 26 weeks, as documented by medical records, treated with quetiapine and mood stabilizer (lithium or valproate). The patients should have had at least 1 manic, depressed or mixed episode in the 2 years prior to the index episode.

Duration of treatment

The study consisted of enrollment and 2 phases: open-label treatment phase (12 weeks to 36 weeks), and randomized treatment phase (up to 104 weeks).

Efficacy

Primary outcome variable: time to recurrence of a mood event

RESULTS:

Patient population
There were 1953 patients enrolled into the study, 1938 received open-label treatment with quetiapine, and thus were included in the open-label safety population. Of the 1953 enrolled patients, 1324 patients were discontinued during open-label treatment, and 1 patient finished the 12- to 36-week open-label treatment phase but was not randomized. Thus, 628 patients were randomized to treatment with quetiapine or placebo used as adjunct to a mood stabilizer (lithium or valproate), 5 of whom did not receive any randomized study medication, so 623 patients were included in the randomized safety population (310 receiving quetiapine and 313 receiving placebo). Of those, all 623 were included in the ITT population, the primary population for analyses of efficacy results.

In patients with bipolar I disorder, quetiapine as adjunct with a mood stabilizer (lithium or valproate) significantly increased the time to recurrence of a mood event (manic or depressed) compared to placebo adjunct with a mood stabilizer. Kaplan-Meier estimates of time to 20 percent of the patients experiencing recurrence of a mood event was 220 days for the quetiapine treatment group and 29 days for the placebo treatment group.

Sponsor Efficacy results, randomized treatment phase (ITT

population)

Outcome variable	QTP + LI/VAL vs PLA + LI/VAL NQTP =360 / NPLA =400 Hazard ratio (95% CI)	P-value
Time to recurrence of a mood event	0.32 (0.24, 0.42)	<0.0001
Time to recurrence of a manic event	0.30 (0.18, 0.49)	<0.0001
Time to recurrence of a depressed event	0.33 (0.23, 0.48)	<0.0001

Analysis using Cox's proportional hazards model with the assigned mood stabilizer and region within study included as covariates.
ITT Intention-to-Treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients i treatment group. CI Confidence interval.

Sponsor Summary of efficacy results prior to mood events, LS means and treatment comparisons of rating scales (ITT population)

Outcome variable	LS mean (SE)		Difference in LS means	95% CI	P-value
	QTP + LI/VAL (N = 310)	PLA + LI/VAL (N = 313)			
SDS total score, mean change[a]	0.3 (0.329)	0.3 (0.357)	-0.5	-1.45, 0.45	0.3017
Additional rating scales[b]					
PGWB total score	97.2 (0.564)	96.1 (0.822)	1.1	-0.86, 3.09	0.2664
YMRS total score	4.1 (0.119)	4.9 (0.145)	-0.8	-1.14, -0.41	<0.0001
MADRS total score	5.9 (0.164)	6.8 (0.196)	-0.9	-1.36, -0.36	0.0008
CGI-BP Severity of Illness	1.8 (0.023)	1.9 (0.032)	-0.1	-0.22, -0.06	0.0003
CGI-BP Global Improvement	3.5 (0.065)	3.6 (0.069)	-0.1	-0.24, 0.13	0.5650
PANSS-P score	8.3 (0.065)	8.4 (0.068)	-0.2	-0.37, 0.00	0.0521

[a] Analysis of the mean change from randomization across all assessment after randomization and up to, but excluding the first mood event, using an ANCOVA model
[b] Analysis of all assessments between randomization and up to, but excluding the first mood event, using a repeated measures mixed model
ITT Intention-to-Treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. SD Standard deviation. SDS Sheehan Disability Scale. PGWB Psychological General Well-being Scale. CGIBP Clinical Global Impression – Bipolar. MADRS Montgomery-Asberg Depression Rating Scale. PANSS-S Positive and Negative Syndrome Scale-Positive Subscale. YMRS Young Mania Rating Scale.

10.2 Line-by-Line Labeling Review

Please see section 9.4.

10.3 SAEs

Table S 17 **Serious non-fatal adverse events ongoing at randomization or reported during RTP (randomized safety population)**

	126+127					
	Randomized treatment		Assigned mood stabilizer			
	QTP+ LI/VAL (N=646)	PLA+ LI/VAL (N=680)	QTP+ LI (N=274)	PLA+ LI (N=287)	QTP+ VAL (N=372)	PLA+ VAL (N=393)
MEDDRA PREFERRED TERM *	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
SUICIDAL IDEATION	3 (0.5)	3 (0.4)	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.5)
DEPRESSION	2 (0.3)	1 (0.1)	2 (0.7)	0	0	1 (0.3)
ANAEMIA	1 (0.2)	0	0	0	1 (0.3)	0
ANGER	1 (0.2)	0	0	0	1 (0.3)	0
ARTHRALGIA	1 (0.2)	0	1 (0.4)	0	0	0
BENIGN PROSTATIC HYPERPLASIA	1 (0.2)	0	1 (0.4)	0	0	0
BIPOLAR I DISORDER	1 (0.2)	0	1 (0.4)	0	0	0
CHOLECYSTITIS	1 (0.2)	0	1 (0.4)	0	0	0
CHOLELITHIASIS	1 (0.2)	0	1 (0.4)	0	0	0
COLON ADENOMA	1 (0.2)	0	1 (0.4)	0	0	0
CONVERSION DISORDER	1 (0.2)	0	1 (0.4)	0	0	0
DIABETIC KETOACIDOSIS	1 (0.2)	0	0	0	1 (0.3)	0
DRUG TOXICITY	1 (0.2)	0	1 (0.4)	0	0	0
HYPERCALCAEMIA	1 (0.2)	0	1 (0.4)	0	0	0
HYPERGLYCAEMIA	1 (0.2)	0	0	0	1 (0.3)	0
HYPONATRAEMIA	1 (0.2)	0	0	0	1 (0.3)	0
MALIGNANT MELANOMA	1 (0.2)	0	0	0	1 (0.3)	0
MANIA	1 (0.2)	1 (0.1)	1 (0.4)	0	0	1 (0.3)
MIGRAINE	1 (0.2)	0	0	0	1 (0.3)	0
MILK-ALKALI SYNDROME	1 (0.2)	0	1 (0.4)	0	0	0

Table S 17 **Serious non-fatal adverse events ongoing at randomization or reported during RTP (randomized safety population)**

	126+127					
	Randomized treatment		Assigned mood stabilizer			
	QTP+ LI/VAL (N=646)	PLA+ LI/VAL (N=680)	QTP+ LI (N=274)	PLA+ LI (N=287)	QTP+ VAL (N=372)	PLA+ VAL (N=393)
MEDDRA PREFERRED TERM [a]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
MUSCLE SPASMS	1 (0.2)	0	0	0	1 (0.3)	0
NAUSEA	1 (0.2)	0	1 (0.4)	0	0	0
OBSTRUCTIVE CHRONIC BRONCHITIS WITH ACUTE EXACERBATION	1 (0.2)	0	1 (0.4)	0	0	0
OEDEMA PERIPHERAL	1 (0.2)	0	1 (0.4)	0	0	0
OSTEOMYELITIS	1 (0.2)	0	1 (0.4)	0	0	0
POSTOPERATIVE INFECTION	1 (0.2)	0	1 (0.4)	0	0	0
PYREXIA	1 (0.2)	0	1 (0.4)	0	0	0
RENAL FAILURE	1 (0.2)	0	0	0	1 (0.3)	0
RENAL FAILURE ACUTE	1 (0.2)	0	1 (0.4)	0	0	0
STRIDOR	1 (0.2)	0	1 (0.4)	0	0	0
TENDON INJURY	1 (0.2)	0	1 (0.4)	0	0	0
THERAPEUTIC AGENT TOXICITY	1 (0.2)	0	1 (0.4)	0	0	0
UPPER LIMB FRACTURE	1 (0.2)	0	1 (0.4)	0	0	0
VISION BLURRED	1 (0.2)	0	0	0	1 (0.3)	0
ABSCESS LIMB	0	1 (0.1)	0	0	0	1 (0.3)
ADENOVIRUS INFECTION	0	1 (0.1)	0	1 (0.3)	0	0
ALCOHOL WITHDRAWAL SYNDROME	0	1 (0.1)	0	0	0	1 (0.3)
ANGINA PECTORIS	0	1 (0.1)	0	0	0	1 (0.3)
ANKLE FRACTURE	0	1 (0.1)	0	0	0	1 (0.3)
APPENDICITIS	0	1 (0.1)	0	1 (0.3)	0	0

Table S 17 Serious non-fatal adverse events ongoing at randomization or reported during RTP (randomized safety population)

	126+127					
	Randomized treatment		Assigned mood stabilizer			
	QTP+ LI/VAL (N=646)	PLA+ LI/VAL (N=680)	QTP+ LI (N=274)	PLA+ LI (N=287)	QTP+ VAL (N=372)	PLA+ VAL (N=393)
MEDDRA PREFERRED TERM *	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ASTHMA	0	2 (0.3)	0	0	0	2 (0.5)
ATRIOVENTRICULAR BLOCK THIRD DEGREE	0	1 (0.1)	0	1 (0.3)	0	0
CARDIAC FAILURE	0	1 (0.1)	0	0	0	1 (0.3)
CELLULITIS	0	1 (0.1)	0	0	0	1 (0.3)
COMA	0	1 (0.1)	0	0	0	1 (0.3)
CYSTITIS	0	1 (0.1)	0	0	0	1 (0.3)
DEEP VEIN THROMBOSIS	0	1 (0.1)	0	0	0	1 (0.3)
DEHYDRATION	0	1 (0.1)	0	1 (0.3)	0	0
DRUG INTERACTION	0	1 (0.1)	0	1 (0.3)	0	0
DYSPHONIA	0	1 (0.1)	0	1 (0.3)	0	0
ELECTROCARDIOGRAM T WAVE ABNORMAL	0	1 (0.1)	0	0	0	1 (0.3)
FACE INJURY	0	1 (0.1)	0	0	0	1 (0.3)
GLYCOSYLATED HAEMOGLOBIN INCREASED	0	1 (0.1)	0	0	0	1 (0.3)
HEPATITIS ACUTE	0	1 (0.1)	0	0	0	1 (0.3)
HYPERTENSION	0	1 (0.1)	0	0	0	1 (0.3)
INFLAMMATORY BOWEL DISEASE	0	1 (0.1)	0	0	0	1 (0.3)
PARANOIA	0	1 (0.1)	0	0	0	1 (0.3)
PNEUMONIA	0	1 (0.1)	0	1 (0.3)	0	0
RIB FRACTURE	0	1 (0.1)	0	1 (0.3)	0	0
THYROID ADENOMA	0	1 (0.1)	0	0	0	1 (0.3)

Table S 17 Serious non-fatal adverse events ongoing at randomization or reported during RTP (randomized safety population)

	126+127					
	Randomized treatment		Assigned mood stabilizer			
	QTP+ LI/VAL (N=646)	PLA+ LI/VAL (N=680)	QTP+ LI (N=274)	PLA+ LI (N=287)	QTP+ VAL (N=372)	PLA+ VAL (N=393)
MEDDRA PREFERRED TERM *	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
URINARY TRACT INFECTION	0	1 (0.1)	0	1 (0.3)	0	0

* Patients with multiple events falling under the same preferred term are counted only once in that term.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. n Number of patients. MedDRA Medical Dictionary of Regulatory Activities. 126 D1447C00126. 127 D144700127. Note: Events ongoing at randomization or reported during randomized treatment phase by decreasing frequency in the QTP+LI/VAL group.
Table corresponds to Table SA 177.

REFERENCES

I have no references to list.

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/s/

Earl Hearst
3/31/2008 01:53:05 PM
MEDICAL OFFICER

Robert Levin
4/10/2008 02:17:17 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-639/S-037

CHEMISTRY REVIEW(S)

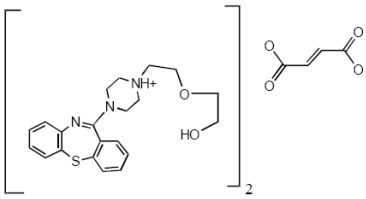
Division of Post Approval Marketing Evaluation IV
Chemist Review of Supplement

1. Division of Post Approval Marketing IV
2. NDA Number: 20639 SE1-037
3. Supplement Numbers/Dates:
   Letter Date: July 19, 2007
   Stamp Date: July 19 2007
4. Amendments/Reports/Dates:
5. Received by Chemist: August 27, 2007

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

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 $C_{42}H_{50}N_6O_4S_2.C_4H_4O_4$



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)

15. Comments: This efficacy supplement for Seroquel® Tablets proposes a maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex. There are no CMC changes proposed. However, an environmental assessment has been submitted by the Sponsor and has been reviewed (by Raanan Bloom, Ph.D. December 11, 2007). As per the EA, the maximum quantity of quetiapine fumarate produced for direct use based on all AstraZeneca drug products, containing quetiapine within the next 5 years is expected to be (b) (4) kg/yr in 2011. Dr Bloom has recommended a Finding of No Significant Impact (FONSI), based on the evaluation of the information provided in this and previous EAs for Seroquel® and further, that no adverse effects are expected from the introduction of quetiapine fumarate into the environment due to the use of Seroquel.

16. Conclusions: **Adequate**. Since there are no CMC changes and the EA is recommended as FONSI (R. Bloom, Ph.D., December 11, 2007), then from the CMC standpoint, this sNDA is recommended for approval.

Recommendations: Recommend Approval of this sNDA.

17. Reviewer Name Julia C. Pinto, Ph.D., Chemist

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

/s/

Julia Pinto
3/5/2008 11:44:55 AM
CHEMIST

Jim Vidra
3/5/2008 02:44:15 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-639/S-037

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT

and

FINDING OF NO SIGNIFICANT IMPACT

for

Seroquel® (quetiapine fumarate) 25, 50, 100, 150, 200, 300, and 400 mg tablets for maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex

sNDA 20-639

Food and Drug Administration
Center for Drug Evaluation and Research

December 11, 2007

FINDING OF NO SIGNIFICANT IMPACT

for

sNDA 20-639

Seroquel® (quetiapine fumarate)
25, 50, 100, 150, 200, 300, and 400 mg tablets for maintenance treatment
of bipolar I disorder as adjunct therapy to lithium or divalproex

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and concluded that this action will not have a significant impact on the quality of the human environment. Therefore, an environmental impact statement will not be prepared.

sNDA 20-639 requests approval of Seroquel® Tablets (quetiapine fumarate) for maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex. In support of its new drug application, AstraZeneca Pharmaceuticals LP prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts from the use and disposal of this product.

Quetiapine fumarate and its metabolites and conjugates may enter the aquatic environment from patient use and disposal. The toxicity of quetiapine fumarate to environmental organisms was characterized. The results indicate that the compound and its metabolites and conjugates are not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital or clinic procedures. Empty or partially empty containers from home use typically will be disposed by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY:

Raanan A. Bloom, Ph.D.
Senior Environmental Officer
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

CONCURRED BY:

Jon Clark, M.S.
Associate Director for Policy
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

CONCURRED BY:

Moheb Nasr, Ph.D.
Director, Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment:

Environmental Assessment
Appended Electronic Signature Page

AstraZeneca

Environmental Assessment	
Drug Substance	Quetiapine fumarate
Document No.	CNS.000-170-627
Date	28 February 2007

Environmental Assessment of Quetiapine

Author: Gisela Holm, PhD
Ecotoxicologist
Global SHE Operations

TABLE OF CONTENTS PAGE

1. DATE

28 February 2007

2. NAME OF APPLICANT/PETITIONER

AstraZeneca Pharmaceuticals LP

3. ADDRESS

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

4. DESCRIPTION OF PROPOSED ACTION

4.1 Requested approval

AstraZeneca Pharmaceuticals LP is filing a supplement to NDA 20-639 pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for quetiapine fumarate (Seroquel® 25, 50, 100, 150, 200, 300, and 400 mg tablets) packaged in bottles and hospital unit dose packages. An environmental assessment (EA) is being submitted pursuant to 21 CFR part 25. The EA is compiled in accordance with 'Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications' CDER, CBER, FDA July 1998.

4.2 Need for action

Seroquel® is currently marketed for the treatment of schizophrenia, acute mania and bipolar depression. An application has been filed to register Seroquel® SR tablets.

4.3 Locations of use

Usage of quetiapine fumarate tablets will occur in households, but also in hospitals throughout the United States.

4.4 Disposal sites

Empty or partially empty packages from patient use in the home, U.S. hospitals, pharmacies or clinics will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling.

5. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

5.1 Nomenclature

5.1.1 Established name (U.S. Adopted name - USAN)

Quetiapine fumarate

5.1.2 Brand/Proprietary name/tradename

Seroquel

5.1.3 Chemical names

5.1.3.1 Chemical abstracts (CA) index name

Ethanol[2–(2–[4–(dibenzo[b,f][1,4]– thiazepin–11–yl–1) piperazinyl)ethoxy]– (E)–2–butenedioate(2:1)

5.1.3.2 Systematic chemical name

IUPAC name:

Bis[2–(2–[4–(dibenzo[b,f][1,4]– thiapin –11–yl)piperazin–1–yl] ethoxy) ethanol]fumarate

5.2 Chemical abstracts service (CAS) registration number

Quetiapine fumarate: 111974-72-2

Base: 111974-69-7

5.3 Molecular formula

Quetiapine fumarate consists of two base components and one acid component.

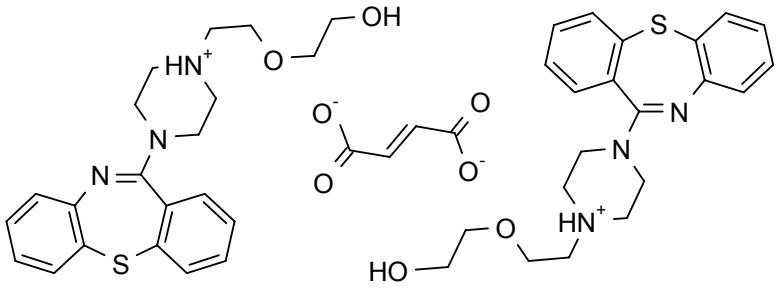
$C_{46}H_{54}N_6O_8S_2$ (quetiapine fumarate)
$C_{21}H_{25}N_3O_2S$ (base)

5.4 Molecular weight

Quetiapine fumarate consists of two base components and one acid component.

883.1 (quetiapine fumarate)
767 (quetiapine = 2 x base)

5.5 Structural (graphic) formula



Quetiapine fumarate

6. ENVIRONMENTAL ISSUES

6.1 Assessing Toxicity to Environmental Organisms

6.1.1 Environmental Fate of Released Substances

6.1.1.1 Identification of Substances of Interest

After oral administration, quetiapine is eliminated almost completely by metabolism, as <1% of the excreted dose can be recovered in urine and faeces as the parent compound (quetiapine) (Appendix I – **Confidential**). Approximately 73% of the dose is excreted as metabolites in urine and 20% is excreted in faeces (Appendix I – **Confidential**). Eleven of the metabolites have been identified, some of which are conjugates of either the metabolites or the parent compound. The conjugates of the parent compound accounts for approximately 1.4% of the given dose. There are two main excreted human metabolites of quetiapine; the sulfoxide acid metabolite (M 289,886) (Fig. 1), and the parent acid metabolite (M 289,663) (Fig. 2). Both metabolites are mainly excreted via urine, but a small amount of each metabolite is also excreted via the faeces. The excretion of M 289,886 altogether represents approximately 28% (24% via urine + 4% via faeces) of the given dose, whereas the excretion of M 289,663 represents approximately 29% (27% + 2%) of the given dose.

The remaining identified excreted metabolites each account for less than 5% of the given dose, except for the sulfoxide (ICI 213,841), which accounts for approximately 6% of the given dose (Appendix I – **Confidential**).

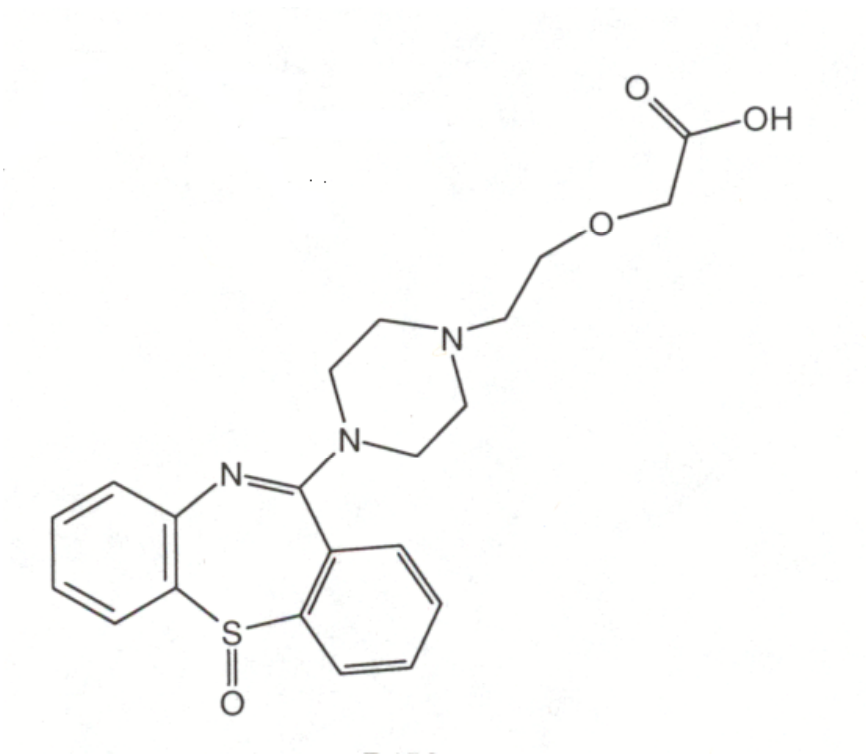


Figure 1. Structural formula for the sulfoxide acid metabolite (M 289,886).

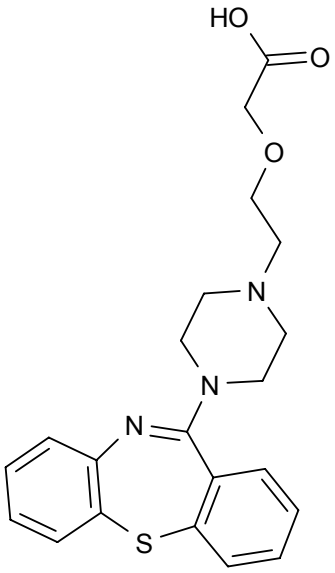


Figure 2. Structural formula for the parent acid metabolite (M 289,663).

The pharmacological effect of the two main excreted metabolites (M 289,886 and M 289,663) was tested *in vitro* (Appendix I – **Confidential**). Neither of these metabolites showed any

pharmacological activity in terms of binding affinity and behavioural tests of dopamine antagonism. Regarding the remaining metabolites, four of them showed potencies similar to or greater than the parent compound. The unconjugated forms of these metabolites represent 4.5% of a given dose. Of particular relevance is the N-desalkylated metabolite (ICI 211,803) which is the major active plasma metabolite in humans. Although it only accounts for approximately 2% of the given dose (excreted via the urine) (Appendix II – **Confidential**), it has significant pharmacological activity in terms of binding affinity at a range of neurotransmitter receptors with potency similar to parent at dopamine D2, but much greater than parent on serotonin 5HT2 and the norepinephrine transporter (Appendix III – **Confidential**).

6.1.1.2 Physical and Chemical Characterization

Water solubility

1600 mg/L at pH 7 (Appendix IV - **Confidential**)

Dissociation constants (pKa) (22°C)

(Appendix V – **Confidential**)

$pKa_1 = 6.8$
$pKa_2 = 3.3$

Octanol/Water Partition Coefficient (25°C)

log K_{ow} = 1.4 at pH 5 (Appendix VI - **Confidential**)
log K_{ow} = 2.7 at pH 7 (Appendix VI - **Confidential**)
log K_{ow} = 2.6 at pH 9 (Appendix VI- **Confidential**)

Vapour pressure

Not determined. Quetiapine is a solid and hence its vapour pressure is assumed to be very low ($<10^{-6}$ Pa).

6.1.1.3 Environmental Depletion Mechanisms

Photolysis
No data.

Biodegradation

Aerobic degradation
The aerobic biodegradation of quetiapine fumarate was assessed according to guideline OECD 301F (Appendix VII - **Confidential**). In this test, aerobic micro-organisms from a sewage treatment works are used to investigate their potential to readily degrade a substance. The results showed that quetiapine fumarate is not readily biodegradable (BOD_{28}/ThOD <0.6).

Anaerobic degradation
The anaerobic biodegradation was assessed according to the UK Department of the Environment test method (Appendix VIII - **Confidential**). The results showed that quetiapine fumarate is not anaerobically biodegradable under the conditions of the test.

Hydrolysis

The stability of quetiapine fumarate in aqueous buffer solutions was assessed according to the US FDA Environmental Assessment (EA) Technical Assistance Document 3.09 (Appendix V – **Confidential**). The extent of hydrolysis at 50°C, at pH 5, 7 and 9, was <10% after 5 days. These data indicate that quetiapine fumarate is hydrolytically stable, with an estimated half-life of ≥1 year at 25°C.

Adsorption to soil

The soil sorption and desorption of quetiapine was assessed according to the US FDA EA Technical Assistance Document 3.08 (Appendix IX – **Confidential**).

Soil type	% organic carbon	% clay	pH	Mean Kd	Mean Koc	% recovery from soil
Nebo	1.6	28	4.9	3600	220,000	1
East Jubilee	2.2	13	5.8	180	8,000	6
Kenny Hill	3.1	14	7.7	45	1,400	19

From the results on the three soils tested, it is evident that the Kd may vary in different soils. However, the data suggests that quetiapine will be essentially immobile.

It should be noted that the Kd values are not proportional to the carbon content, so the Koc is not likely to be a reliable predictor of adsorption to soil (or sewage sludge). It is more likely that the adsorption is dependent on pH, with higher adsorption in more acidic soils. There is also evidence to suggest that the adsorption of quetiapine is irreversible, especially in more acidic soils

6.1.1.4 Environmental Concentrations

The Expected Introduction Concentration (EIC) is based on all AstraZeneca Pharmaceuticals LP drug products containing quetiapine fumarate. See Appendix X – **Confidential**.

6.1.1.5 Summary

The use of quetiapine fumarate is likely to result mainly in metabolites and, to a lesser extent, the active moiety entering the environment, since it is almost completely metabolised after

consumption. The metabolites are mainly excreted *via* urine (73%), and to a lesser extent *via* faeces (20%). Based on the physico-chemical properties of quetiapine fumarate (log K_{ow} 2.7, water solubility = 1600 mg/L and vapour pressure $<10^{-6}$ Pa) it is predicted that most of the active moiety (quetiapine) will be partitioned into the aqueous phase during wastewater treatment. However, the log K_{ow} may not be a very reliable predictor of adsorption and some adsorption to sludge may occur depending on the pH. The aqueous streams containing quetiapine will then subsequently be passed to the aquatic environment. When estimating the Expected Introduction Concentration (EIC), it is assumed that all quetiapine ends up in the aquatic environment, but that only 43% is present in potentially active forms, since it is known that the two major metabolites showed no pharmacological activity when tested *in vitro*.

In the aquatic environment, quetiapine is not likely to be hydrolytically degraded, and there is no evidence to suggest that biodegradation will be significant. However, quetiapine is not likely to bioaccumulate in aquatic organisms.

6.1.2 Environmental Effects of Released Substances

The following ecotoxicological studies were performed with quetiapine fumarate:

Activated sludge, respiration inhibition test

The respiration inhibition of activated sludge was assessed according to the OECD guideline 209 (Appendix XI - **Confidential**).

3 h EC_{50} = 100 mg/L

3 h No observed effect concentration (NOEC) = 100 mg/L

Blue-green alga, *Microcystis aeruginosa*

The toxicity to the blue-green alga, *M. aeruginosa* was assessed according to the FDA Environmental Assessment (EA) Technical Assistance Document 4.01 (Appendix XII – **Confidential**).

Based on the largest specific growth rates during the study (21 days):

No observed effect (P=0.05) concentration (NOEC) = 32 mg/L
Lowest significant effect (P=0.05) concentration = 64 mg/L

Based on maximum cell densities achieved (21 days):

NOEC (P=0.05) = 4.0 mg/L
Lowest significant effect (P=0.05) concentration = 8.0 mg/L

Green alga, *Selenastrum capricornutum*

The toxicity to green alga, (*Selenastrum capricornutum*) was assessed according to the FDA EA Technical Assistance Document 4.01 (Appendix XIII – **Confidential**).

Based on the largest specific growth rates during the study (14 days):

NOEC (P=0.05) = 2.5 mg/L
Lowest significant effect (P=0.05) concentration = 5.0 mg/L

Based on maximum cell densities achieved (14 days):

NOEC (P=0.05) = 2.5 mg/L
Lowest significant effect (P=0.05) concentration = 5.0 mg/L

Water-flea, *Daphnia magna*

The long-term toxicity to *Daphnia magna* was assessed according to the FDA EA Technical Assistance Document 4.09 (Appendix XIV - **Confidential**).

Based on reproduction (21 days):

NOEC = 18 mg/L
Lowest Observed Effect Concentration (LOEC) = 32 mg/L

Based on length (21 days):

NOEC = 18 mg/L
LOEC = 32 mg/L

Rainbow trout (*Oncorhynchus mykiss*)

The toxicity of quetiapine fumarate to rainbow trout was assessed according to the FDA EA Technical Assistance Document 4.11 (Appendix XV - **Confidential**).

96 h LC_{50} = 22.0 mg/L
96 h NOEC = 1.0 mg/L

Bluegill sunfish (*Lepomis macrochirus*)

The toxicity of to rainbow trout was assessed according to the FDA EA Technical Assistance Document 4.11 (Appendix XVI - **Confidential**).

96 h LC_{50} = 19.3 mg/L
96 h NOEC = 1.8 mg/L

According to the short-term ecotoxicological tests, quetiapine fumarate shows low short-term toxicity to fish but no short-term toxicity to micoorganisms in activated sludge. The long-term ecotoxicological tests show toxicity to algae and blue-green algae at mg/L concentration levels. The long-term effect of quetiapine to the water-flea *D. magna* appears to be minor. In addition, there were no observed sublethal effects at the Maximum Expected Environmental Concentration (MEEC).

In summary, the available ecotoxicological data indicate that quetiapine is not very toxic to aquatic organisms.

No rapid, complete depletion mechanism has been identified for quetiapine fumarate. However, the result from the microbial inhibition screening test above indicates that the drug substance does not inhibit respiration of activated sludge microorganisms. Therefore, it is not thought to disrupt wastewater treatment processes. Furthermore, as the log K_{ow} is <3.5 (see Physical and Chemical Characterization), the compound is not likely to bioaccumulate in aquatic organisms.

Based on the NOECs for the different ecotoxicological studies, the most sensitive species is fish. Since data are available for fish, *Daphnia* and algae, a Tier 2 assessment factor of 100 is justified. Hence a safety factor of 100 is applied to the lowest acute LC_{50} of 19.3 mg/L (bluegill sunfish).

96 h LC_{50} = 19.3 mg/L = 19300 µg/L

EC_{50}/EIC (Appendix X - **Confidential**) = 19300/EIC >100 (assessment factor), and no effects were observed at MEEC, i.e. no further testing is needed.

6.1.3 Summary

The intended use of quetiapine fumarate is likely to result mainly in metabolites entering the environment, since it is almost completely metabolised after consumption. Approximately 73% of the metabolites are excreted in the urine and 20% in the faeces. It is predicted that most of the active moiety (quetiapine) will be partitioned into the aqueous phase during wastewater treatment.

In the aquatic environment, quetiapine is not likely to be hydrolytically degraded, and there is no evidence to suggest that biodegradation will be significant. However, quetiapine is not likely to bioaccumulate in aquatic organisms.

Quetiapine fumarate shows short-term toxicity to fish but not to micoorganisms in activated sludge. The long-term studies indicate that quetiapine is not very toxic to aquatic organisms.

When estimating the Expected Introduction Concentration (EIC), it is assumed that all quetiapine ends up in the aquatic environment, but that only 43% is present in potentially active forms, since it is known that the two major metabolites are essentially inactive. The rest of the excreted metabolites were assumed to exhibit the same pharmacological effects as the parent compound, due to the insufficient information available.

The EIC is based on all AstraZeneca Pharmaceuticals LP drug products containing quetiapine (Appendix X – **Confidential**).

Comparing the EIC with the lowest LC_{50} from the most sensitive species (bluegill sunfish) using an assessment factor of 100 gives:

EC_{50}/EIC = 19300 / EIC >100 (assessment factor)

In conclusion, since the ratio of the EC_{50} for the most sensitive of the acute toxicity test organisms to the expected introduction concentration is over two orders of magnitude larger than the assessment factor, and no effects were observed at MEEC, no adverse environmental effects are anticipated as a consequence of the use of quetiapine.

7. MITIGATION MEASURES

No adverse environmental effects are anticipated due to the use of quetiapine fumarate. Therefore, no mitigation measures are needed.

8. ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental effects have been identified for the proposed action. Therefore, no alternatives to the proposed action will be proposed.

9. LIST OF PREPARERS

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10. APPENDICES

10.1 Nonconfidential Appendices

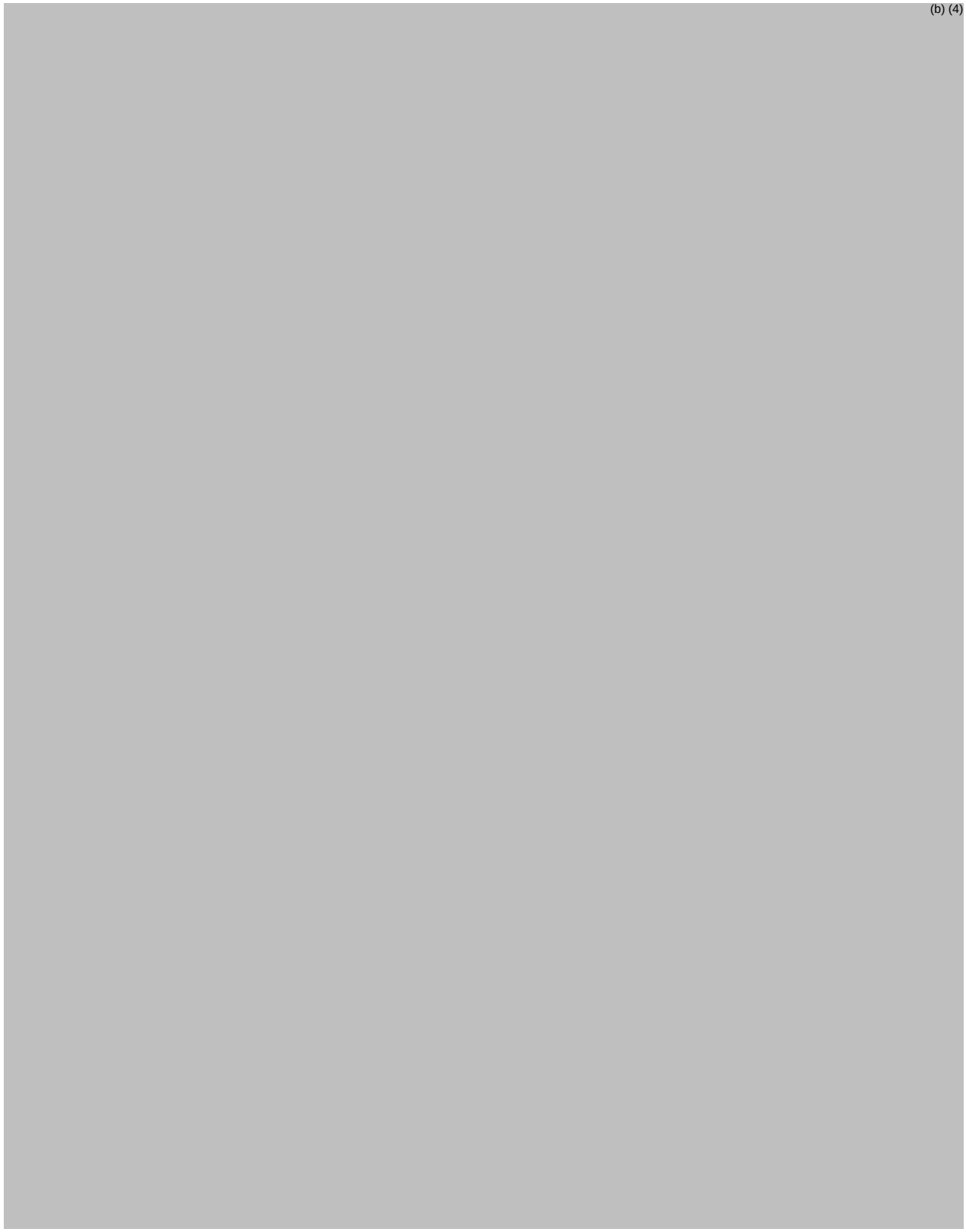
10.1.1 Data Summary Table

All test results from the environmental effect studies are expressed as ppm of quetiapine fumarate.

DATA SUMMARY TABLE FOR QUETIAPINE	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	1600 mg/L (ppm) at pH 7
Dissociation Constants (22°C)	$pKa_1 = 6.8$ $pKa_2 = 3.3$
Log Octanol/Water Partition Coefficient (log K_{ow}) (25°C)	log K_{ow} = 1.4 at pH 5 log K_{ow} = 2.7 at pH 7 log K_{ow} = 2.6 at pH 9
Vapour Pressure or Henry's Law Constant	No data
Sorption / Desorption (K_{oc})	K_{oc} = 220,000 (Nebo) K_{oc} = 8,000 (East Jubilee) K_{oc} = 1,400 (Kenny Hill)
DEPLETION MECHANISMS	
Hydrolysis	t½ at 25°C ≥ 1 year
Aerobic Biodegradation	Not readily biodegradable (BOD_{28}/ThOD <0.6).
Anaerobic degradation	Not degradable
Soil Biodegradation	No data
Photolysis	No data
Metabolism	Almost completely metabolised, <1% of the dose can be recovered as quetiapine

ENVIRONMENTAL EFFECTS	
Microbial Inhibition	No inhibition up to 100 ppm
Acute toxicity	**Rainbow trout** (*Oncorhynchus mykiss*) 96 h LC50 = 22.0 ppm 96 h NOEC = 1.0 ppm **Bluegill sunfish** (*Lepomis macrochirus*) 96 h LC50 = 19.3 ppm 96 h NOEC = 1.0 ppm
Chronic Toxicity	**Green alga** (*Selenastrum capricornutum*): Max. cell densities (MCD) 14 d NOEC = 2.5 ppm MCD 14 d lowest significant effect = 5.0 ppm Growth rate 14 d NOEC = 2.5 ppm Growth rate 14 d lowest significant effect = 5.0 ppm **Blue-green alga** (*Microcystis aeruginosa*) MCD 14 d NOEC = 4.0 ppm MCD 14 d lowest significant effect = 8.0 ppm Growth rate 14 d NOEC = 32 ppm Growth rate 14 d lowest significant effect = 64 ppm **Water flea** (*Daphnia magna*): 21 d reproduction NOEC = 18 ppm 21 d reproduction LOEC = 32 ppm 21 d length NOEC = 18 ppm 21 d length LOEC = 32 ppm

10.2 Confidential Appendices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/s/

Jon E. Clark
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: December 11, 2007

From: Raanan A. Bloom, Ph.D.
OPS/IO/PARS

To: Teshara G. Bouie
OPS/ONDQA/DPMA

Through: Jon Clark, M.S.
OPS/IO/PARS

Subject: Supplemental New Drug Application (sNDA) for Seroquel® (quetiapine fumarate) Tablets for maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex.

sNDA 20-639
Submission Date (Cover Letter): July 19, 2007

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Background

Seroquel (quetiapine fumarate) Tablets (NDA 020-639) is currently indicated for the treatment of schizophrenia and for the treatment of depressive episodes associated with bipolar disorder and acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex.

The present sNDA has been submitted for an indication of maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex. Pursuant to 21 CFR part 25, an environmental assessment (EA), dated February 28, 2007, has been submitted in support of the application.

Quetiapine fumarate formulated as Seroquel SR tablets is also approved under NDAs 22-047 and 22-172.

Review of the Current Submission

The EA was prepared in accordance with 21 CFR 25. The EA provides the same information as was provided in the EAs submitted under NDAs 22-047 and 22-172. These EAs provided an estimate of quetiapine fumarate produced for direct use for all dosage forms and strengths for all of AstraZeneca's related applications. The present sNDA does not significantly alter this estimate. A full review of the EA may be found in the November 9, 2006, review memorandum under NDA 22-047. A Finding of No significant Impact (FONSI) was issued for NDA 22-047 on November 9, 2006 and for NDA 22-172 on August 20, 2007.

The environmental fate and effects data referenced in the EAs were previously submitted in an EA for NDA 20-639/S-016 and S-017 (December 30, 2002), which was reviewed and found adequate by Florian Zielinski (January 28, 2003).

Based on the EA submitted with this application, the maximum quantity of quetiapine fumarate produced for direct use based on all AstraZeneca Pharmaceuticals LP drug products containing quetiapine in any of the next 5 years is expected to be (b) (4) kg/yr in 2011. The calculation includes the largest projected production forecast for direct use, per year, in the US market for the years 2007 to 2011 inclusive. The calculated Expected Introduction Concentration (EIC) of quetiapine is (b) (4) ppb. The sales volume presented is a slight decrease from the amount projected under NDAs 22-047 and 22-172 ((b) (4) kg; EIC (b) (4) ppb).

Data previously submitted in the related EAs includes ecotoxicological studies of fish, daphnia, and algae. The most sensitive species tested is the bluegill sunfish. The EC_{50}/EIC ratio for the bluegill sunfish is (b) (4), which is greater than (b) (4) In addition the EIC is lower than the NOEC for each of the species tested. This assessment indicates that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

Comments and Conclusions

Based on an evaluation of the information provided in this and previous EAs for Seroquel and in FDA guidance, no further testing is required and no adverse effects are expected from the introduction of quetiapine fumarate into the environment due to the use of Seroquel.

A Finding of No Significant Impact (FONSI) is recommended.

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/s/

Raanan Bloom
12/11/2007 03:52:30 PM
ENV ASSESSMENT

Jon E. Clark
12/13/2007 10:35:22 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-639/S-037

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#037
Drug Name:	Quetiapine
Indication(s):	Bipolar I
Applicant:	Astra Zeneca
Date(s):	Initial submission date: July 19, 2007
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	George Kordzakhia, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.; H.M. James Hung, Ph.D.
Medical Division:	Division of Psychiatry Products
Clinical Team:	Earl Hearst, M.D., Reviewer Ni Khin, M.D., Team Leader
Project Manager:	Doris Bates
Key Words	Cox-proportional hazard model

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

When used as adjunct with a mood stabilizer (lithium or valproate) the quetiapine fumarate treatment arm (oral tablets 400mg to 800mg daily in divided doses) showed positive maintenance effect compared with placebo for adult patients with Bipolar I Disorder (as measured by time to mood event).

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor submitted results of two pivotal studies D1447C00126 and D1447C00127 in support of efficacy of quetiapine.

Studies 126 and 127 were multicenter, randomized, parallel-group, double-blind studies to compare quetiapine with placebo when used as adjunct to lithium or valproate in the maintenance treatment of adult patients with bipolar I disorder for up to 104 weeks. Both studies had the same design. Study 127 was conducted in USA and Canada, and Study 126 was international study (18 countries in Europe, Eastern Europe, Asia, Africa, Australia, and Northern America).

A total of 1461 patients entered Study126, 706 patients were randomized and 347 patients completed the study. The most common reasons for discontinuing the study were mood event and patient decision.

There were 1953 enrolled patients in Study127, 628 patients were randomized and 176 patients completed the study. The most common reasons for discontinuing the study were mood event patient decision and lost to follow up.

1.3 STATISTICAL ISSUES AND FINDINGS

In studies 126 and 127, quetiapine treatment arms (oral tablets 400mg to 800mg daily in divided doses) were statistically superior to corresponding placebo arms with respect to time to mood event when used as adjunct with a mood stabilizer (lithium or valproate). The p-values obtained from Cox-proportional hazard model were < 0.001. The sponsor wants to claim statistical significance of quetiapine on secondary endpoints: time to manic event and time to depressed event. However, the studies were not designed to collect time to first manic event and first depressed event separately. The primary efficacy endpoint (time to mood event) is a composite endpoint, defined as time to manic, depressed or mixed episode, whichever comes first. If a patient has a mood event due to a depressed episode, the time to first manic event would need to be censored on the date of the depressed episode and vice versa. Because of this issue, the results on these individual components as key secondary endpoints are difficult to interpret.

2 INTRODUCTION

2.1 OVERVIEW

The sponsor submitted results of two pivotal studies (D1447C00126 and D1447C00127) in support of long-term efficacy of quetiapine when used as adjunct with a mood stabilizer (lithium or valproate) in the maintenance treatment of adult patients with Bipolar I Disorder for up to 104 weeks.

2.2 DATA SOURCES

Data used for review are from the electronic submission received on July 19, 2007. The network path is \\Cdsesub1\nonectd\N20639\S_037\2007-07-19 in the EDR.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 OBJECTIVE

For Studies 126 and 127, the primary objective was to evaluate the efficacy of quetiapine versus placebo when used as adjunct to mood stabilizer (lithium or valproate) in increasing time to recurrence of a mood event.

3.1.2 STUDY DESIGN

Studies 126 and 127 were multicenter, randomized, parallel-group, double-blind studies to compare quetiapine with placebo when used as adjunct to lithium or valproate in the maintenance treatment of adult patients with bipolar I disorder for up to 104 weeks.

To be eligible for the studies a patient had to have an acute manic, depressed or mixed episode at enrollment or have had a past manic, depressed or mixed episode within 26 weeks, as documented by medical records, treated with quetiapine and mood stabilizer (lithium or valproate). Both studies consisted of enrollment and 2 phases, the initial open-label treatment phase and the subsequent randomized treatment phase.

To be eligible for randomization, a patient must have been treated with quetiapine within the range of 400 to 800 mg/day and mood stabilizer (lithium or valproate) for at least 12 weeks up to 36 weeks during the open-label treatment phase. To be randomized, a patient also had to have a YMRS total score ≤12, and a MADRS total score ≤12 assessed at a minimum of 4 consecutive visits spanning ***at least 12 weeks***, with the allowance of a single excursion with a YMRS and/or MADRS total score of 13 or 14 (unless this occurred on the last of the 4 consecutive visits).

Table 1. Chart for Studies 126 and 127.

Enrollment	Open-label treatment Phase	Randomized treatment Phase
Up to 7 days	12 to 36 weeks	Up to 104 weeks
	Open-label quetiapine plus mood stabilizer	
Visit S0	Visit S1 up to Visit S12	Visits 1-23

Source: Corresponds to Figure 1 (pg 63), Clinical Study Report D1447C00126 and Figure 1(pg 64), Clinical Study Report D1447C00127

Enrollment: The enrollment process could last for up to 7 days. At the first visit (Visit S0), patients, or a legally acceptable representative, provided informed consent and subsequently completed all required laboratory and clinical evaluations. Patients who met all inclusion criteria and none of the exclusion criteria were enrolled into the open-label treatment phase at Visit S1, which had to occur within 7 days of Visit S0. If the enrollment exceeded 7 days, all evaluations had to be repeated before the patient could enter the open-label treatment phase.

Open-label treatment phase: The purpose of the open-label treatment phase was to achieve stabilization and confirm stability of the patient's clinical condition and of the dosages of quetiapine and mood stabilizer before randomization. Patients had to be treated with quetiapine and mood stabilizer (lithium or valproate) for a minimum of 12 weeks (up to 36 weeks) before being eligible to meet the criteria for randomization. To be randomized, a patient also had to have a YMRS total score ≤12, and a MADRS total score ≤12 assessed at a minimum of 4 consecutive visits spanning at least 12 weeks.

The first dose of open-label treatment was dispensed at the first visit (Visit S1) after Visit S0. Visits occurred monthly with an option to perform additional visits at week 1 (Visit S2) and week 2 (Visit S3), depending on the patient's clinical condition, as judged by the investigator.

During the open-label treatment phase, patients were treated with open-label quetiapine (400-800 mg daily in divided doses with a recommended target dose of 600 mg) and a mood stabilizer (lithium or valproate with a trough serum concentration of 0.5 mEq/L to 1.2 mEq/L for lithium and 50 μg/ml to 125 μg/ml for valproate) chosen by the investigator according to his or her clinical judgement. Other antipsychotic and psychoactive medications (eg, antidepressants and anxiolytics) could also be used as clinically indicated during this phase, with exception of the last 12 weeks prior to randomization.

Randomized treatment phase: Patients who met all the inclusion criteria for randomization and none of the exclusion criteria for randomization were randomized (at Visit 1) in a blinded fashion to quetiapine or placebo twice daily (400-800 mg daily in divided doses with a recommended target dose of 600 mg) plus open-label mood stabilizer (lithium or valproate) with a trough serum concentration of 0.5 mEq/L to 1.2 mEq/L for lithium and 50 μg/ml to 125 μg/ml for valproate). Starting at Visit 1 (the day of randomization), open-label 100 mg quetiapine tablets would be replaced with 100 mg tablets of blinded investigational product at a rate of 1 tablet per every 2 days. Randomization was stratified by assigned mood stabilizer (lithium or valproate). Patients continued in the randomized treatment phase for up to 104 weeks, or until they met any of the criteria for a mood event (manic, depressed or mixed), or until the study was terminated by AstraZeneca. Once a mood event occurred, the patient had to be discontinued from the study. The mood event was reported to the monitor within 3 days of event onset. Patients could also be discontinued from study treatment and assessments due to lack of efficacy, adverse event, patient lost to follow-up, protocol noncompliance, informed consent withdrawn, or other.

3.1.3 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Study 126

The study was conducted in 177 study sites in 18 countries (Australia, Belgium, Bulgaria, Czech Republic, Finland, France, Germany, Hungary, Italy, Norway, Poland, Russia, Spain, Sweden, Turkey, UK, US and South Africa). The first patient entered the study on 06 April 2004 and the last patient completed the study on 31 October 2006. There were 1461 patients enrolled into the study, 1433 received open-label treatment with quetiapine, and thus were included in the open-label safety population. Of the 1461 enrolled patients, 706 patients were randomized to treatment with quetiapine or placebo used as adjunct to a mood stabilizer (lithium or valproate), 3 of whom did not receive any randomized study medication, so 703 patients were included in the randomized safety population (336 receiving quetiapine and 367 receiving placebo). Of those, all 703 were included in the ITT population, the primary population for analyses of efficacy results. Of the 703 patients in the ITT population, 242 (34.4%) patients had treatment discontinued due to a mood event, 347 patients (49.4%) completed the randomized treatment (either the maximum 104 weeks or up to the time when study was terminated by AstraZeneca).

Table 2. Study 126 Patient Disposition (Randomized Treatment Phase)

Patients Randomized: N=706	**Quetiapine+LI/VAL**	**Placebo+ LI/VAL**
ITT and Safety Population: N=703	336	367
Discontinued due to a mood event	62	180
Discontinued for reason other than a mood event	61	53
Subject not willing to continue	26	16
Adverse event	8	9
Lack of therapeutic response	0	1
Eligibility criteria not fulfilled	6	7
Lost to follow up	5	6
Other	16	14
Completed treatment	213	134

Source: Clinical Study Report D1447C00126, Figure 4 (pg 126)

Table 3 summarizes baseline physical characteristics (gender, ethnic origin, age, and weight) and YMRS and MADRS scores at randomization for ITT population. The ITT population was well balanced regarding gender (approximately 55% female), and age (approximately 42 years old). The patients were predominantly Caucasian (approximately 97%). Overall, the mean weight of the ITT population at randomization was 84.1 kg. Treatment arms appeared comparable with respect to the baseline physical characteristics and baseline YMRS and MADRS scores.

Table 3. Study 126 Demographic and Baseline characteristics (ITT population)

Variable	QTP+ LI/VAL N=336	PLA+ LI/VAL N=367	Total N=703
Gender			
Male	144 (42.9 %)	172 (46.9%)	316 (45%)
Female	192 (57.1%)	195 (53.1%)	387 (55.0%)
Age (years)			
Mean (SD)	42.26 (12.50)	41.93 (12.82)	42.09 (12.66)
Median	43.00	41.00	42.00
Min to Max	18 to 75	18 to 84	18 to 84
Age Distribution			
18-39 years	138 (41.1%)	162 (44.1%)	300 (42.7%)
40-65	190 (56.5%)	194 (52.9%)	384 (54.6%)
>65	8 (2.4%)	11 (3.0%)	19 (2.7%)
Origin			
Caucasian	321 (95.5%)	358 (97.5%)	679 (96.6%)
African	8 (2.4%)	3 (0.8%)	11 (1.6%)
Oriental	2 (0.6%)	1 (0.3%)	3 (0.4%)
Other	5 (1.5%)	5 (1.4%)	10 (1.4%)
Weight (kg)			
Mean (SD)	84.58 (18.03)	83.66 (18.53)	84.10 (18.29)
Median	83.00	82.00	82.20
Min to Max	45 to 145	46 to 165	45 to 165
YMRS (at randomization)			
Mean (SD)	2.47 (3.05)	2.24 (2.81)	2.35 (2.93)
Median	1.00	1.00	1.00
Min to Max	0, 12	0, 12	0, 12
MADRS (at randomization)			
Mean (SD)	3.38 (3.52)	3.68 (3.79)	3.54 (3.67)
Median	2.50	3.00	3.00
Min to Max	0, 17	0, 30	0, 30

Source: Clinical Study Report D1447C00126, Table 11.1-7 (pg 285-286), Table 11.1-13 (pg 296)

Study 127

The study was conducted in 127 study centers in the United States and Canada. The first patient entered the study on 2 March 2004 and the last patient completed the study on 18 September 2006. In total, 1953 patients were enrolled at 102 study sites (of the 127 total participating sites that were initiated) and 628 patients (32.2% of the enrolled patients) were randomized. Of the 628 randomized patients, 5 patients (0.8%) did not receive study drug after randomization and were excluded from the randomized safety population. Of the 623 patients in the ITT population, 226 patients (36.3%) had treatment discontinued due to a mood event, 221 patients (35.5%) had the randomized treatment discontinued for reasons other than a mood event, and 176 patients (28.3%) completed the randomized treatment (either the maximum 104 weeks or up to the study termination by AstraZeneca).

Table 4. Study 127 Patient Disposition (Randomized Treatment Phase)

Patients Randomized: N=628	**Quetiapine+LI/VAL**	**Placebo+ LI/VAL**
ITT and Safety Population: N=623	310	313
Discontinued due to a mood event	63	163
Discontinued for reason other than a mood event	137	84
Subject not willing to continue	32	26
Adverse event	35	8
Lack of therapeutic response	2	0
Eligibility criteria not fulfilled	8	5
Lost to follow up	30	25
Other	30	20
Completed treatment	110	66

Source: Clinical Study Report D1447C00127, Figure 4 (pg 125)

The demographic and key baseline characteristics of the patients evaluable for the primary analysis of efficacy in the randomized treatment phase (the ITT population) are summarized in Table 5. There were no major imbalances between the treatment groups with regards to demography and baseline YMRS and MADRS scores. The mean age in the ITT population was about 40 years old and well balanced with regard to gender. They were predominantly Caucasian (about 82%), and about 13% were Black. Overall, the mean weight of the ITT population at randomization was 92.7 kg. The quetiapine treatment group was similar in age to the placebo group and slightly heavier (mean weight 94.3 kg compared to 91.2 kg).

Table 5. Study 127 Demographic and Baseline characteristics (ITT population)

Variable	QTP+ LI/VAL N=310	PLA+ LI/VAL N=313	Total N=623
Gender			
Male	151 (48.7%)	145 (46.3%)	296 (47.5%)
Female	159 (51.3%)	168 (53.7%)	327 (52.5%)
Age (years)			
Mean (SD)	40.59 (11.70)	39.61 (11.72)	40.10 (11.71)
Median	42.00	39.00	40.00
Min to Max	18 to 75	19 to 74	18 to 75
Age Distribution			
18-39 years	136 (43.9%)	165 (52.7%)	301 (48.3%)
40-65	171 (55.2%)	144 (46.0%)	315 (50.6%)
>65	3 (1.0%)	4 (1.3%)	7 (1.1%)
Origin			
Caucasian	248 (80.0%)	261 (83.4%)	509 (81.7%)
African	46 (14.8%)	34 (10.9%)	80 (12.8%)
Oriental	4 (1.3%)	3 (1.0%)	7 (1.1%)
Other	12 (3.9%)	15 (4.8%)	27 (4.3%)
Weight (kg)			
Mean (SD)	94.28 (22.06)	91.15 (19.47)	92.71 (20.84)
Median	92.60	89.70	91.00
Min to Max	46 to 182	50 to 170	46 to 182
YMRS (at randomization)			
Mean (SD)	3.6 (3.14)	3.5 (3.15)	3.5 (3.64)
Min to Max	0, 15	0, 13	0, 15
MADRS (at randomization)			
Mean (SD)	5.0 (3.68)	4.6 (3.59)	4.8 (3.64)
Min to Max	0, 18	0, 12	0, 18

Source: Clinical Study Report D1447C00127, Table 17 (pg 129-130), Table S1 (pg. 8)

3.1.4 STATISTICAL METHODOLOGIES

The analyses of efficacy data were primarily based on the ITT population which included all randomized patients with baseline and postbaseline observations. In addition, a supportive analysis was carried out using the PP population to evaluate the robustness of the results.

For Studies 126 and 127, the primary analysis was based on time to first recurrence of a mood event, and the statistical model used in this analysis was a Cox regression model. This model uses the primary variable (time to mood event) to estimate a hazard ratio, which is the outcome of the model. As a complement, Kaplan-Meier estimates and plots were provided (in order to infer the time to mood events).

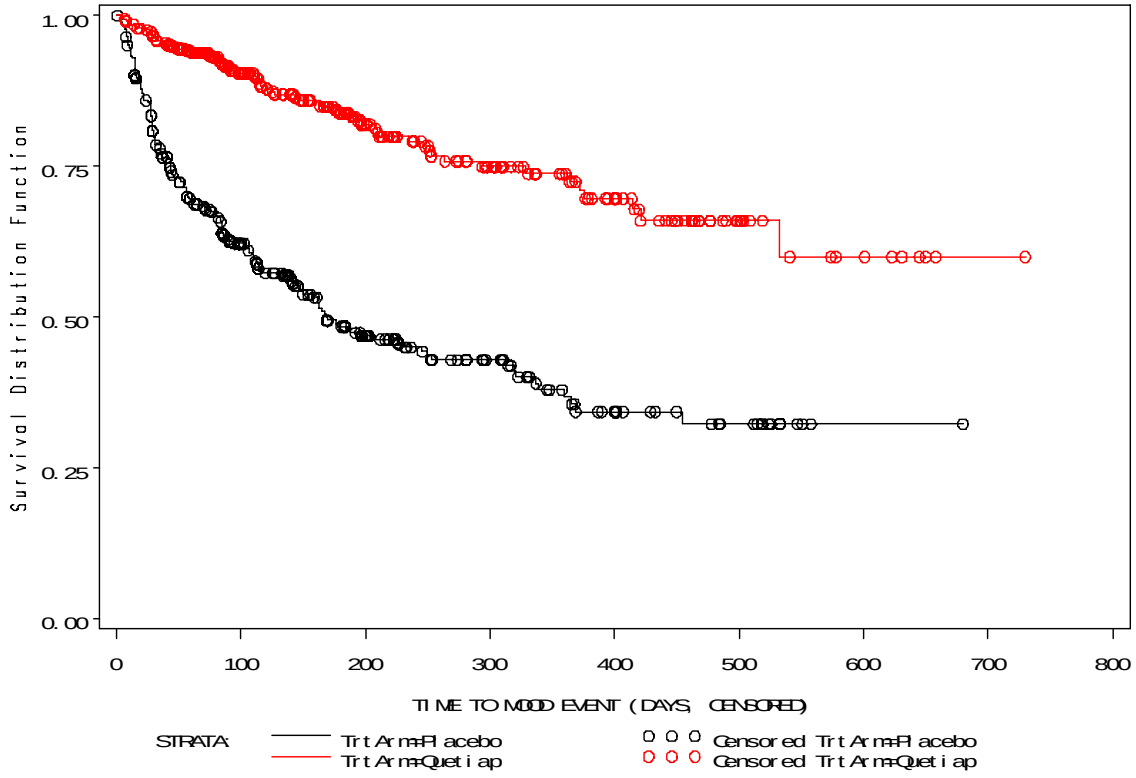
A sensitivity analysis was performed using the stratified Cox model and Log-rank test. For Study 126 the model was stratified by the assigned mood stabilizer and geographical region. For Study 127 the model was stratified by the mood stabilizer.

3.1.5 RESULTS OF EFFICACY ANALYSES

Primary Analysis

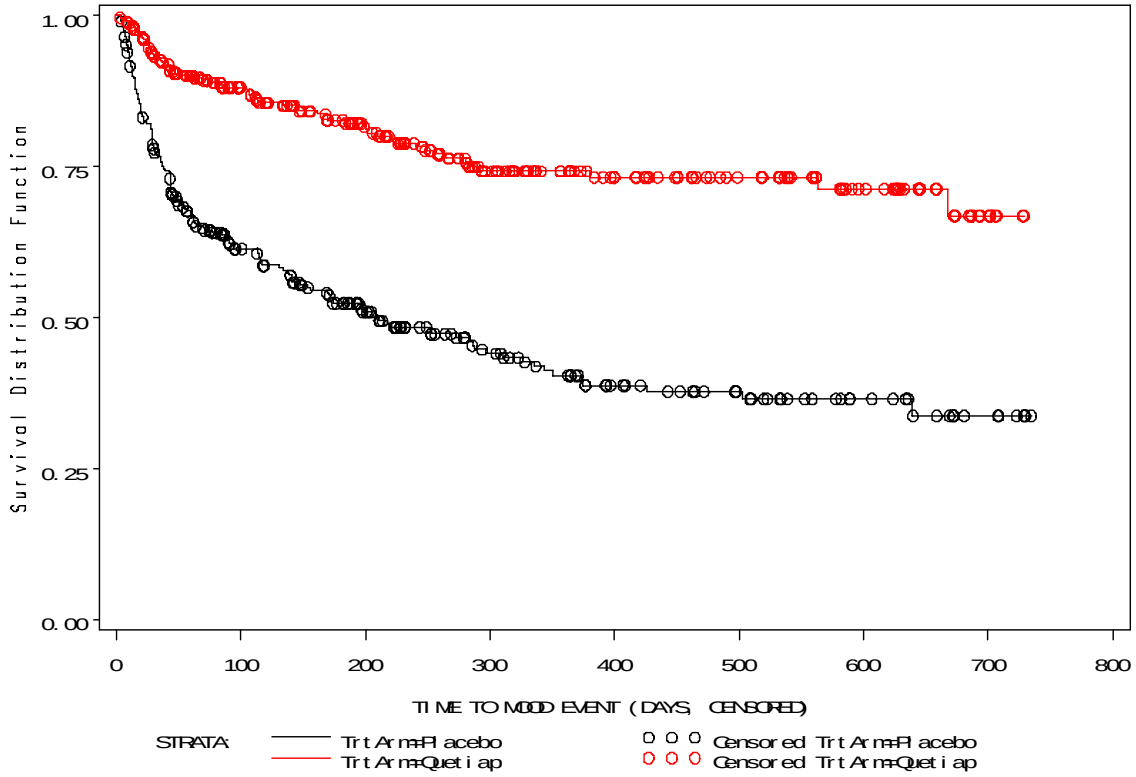
The Cox-proportional hazard analysis of time to recurrence of a mood event showed that quetiapine was superior to placebo when used as adjunct with lithium or valproate in increasing time to recurrence of a mood event. The results are presented in Table 6. For Study 126 the estimated hazard ratio (quetiapine versus placebo) was 0.28 (95% CI = 0.21 to 0.37, p-value <0.0001) corresponding to a hazard rate reduction of 72%. For Study 127, the estimated hazard ratio (quetiapine versus placebo) was 0.32 (95% CI = 0.24 to 0.42, p<0.0001), corresponding to a hazard rate reduction of 68%. For both studies, Kaplan Meier curves for time to recurrence of a mood event support that the mood event rate was lower in the quetiapine treatment group than in placebo treatment group during the entire randomized treatment phase.

Figure 1. Study 126 Kaplan-Meier curves of Time to Mood Event for the randomized treatment phase (curves from top to bottom: Quetiapine, Placebo)



[Source: Reviewer's results]

Figure 2. Study 127 Kaplan-Meier curves of Time to Mood Event for the randomized treatment phase (curves from top to bottom: Quetiapine, Placebo)



[Source: Reviewer's results]

Table 6. Summary of the Patients with Mood Event and Censored Patients

	Study 126		Study 127	
	QTP+LI/VAL	**PLA+LI/VAL**	**QTP+LI/VAL**	**PLA+LI/VAL**
Total number of patients	336 (100%)	367 (100%)	310 (100%)	313 (100%)
Patients who had mood event	62 (18.45%)	180 (49.05%)	63 (20.32%)	163 (52.08%)
Depressed	23 (6.85%)	63 (17.17%)	30 (9.68%)	70 (22.36%)
Manic	29 (8.63%)	71 (19.35%)	16 (5.16%)	39 (12.46%)
Mixed	10 (2.98%)	46 (12.53%)	17 (5.48%)	54 (17.25%)

Source: Reviewer's Results

Table 7. Primary Analysis: Cox-proportional Hazard Analysis of Time to Mood Event

	QTP+LI/VAL vs PLA+LI/VAL	
	Study 126	**Study 127**
Hazard Ratio (HR)	0.28	0.32
95% CI for HR	(0.21, 0.37)	(0.24, 0.42)
p-value	<0.001	<0.001

Source: Clinical Study Report D1447C00126, Table 24 (pg 143); Clinical Study Report D1447C00127 Table 24 (pg 143)

Sensitivity Analysis

For Study 126, Cox-proportional Hazard model and Log-Rank Test stratified by mood stabilizer and region (US, Rest of the World) were considered as sensitivity analysis. For Study 127, stratification was performed by mood stabilizer. For both studies, the results of sensitivity analyses confirmed the conclusions of primary analysis.

Table 8. Sensitivity Analysis: Stratified Cox-proportional Hazard Analysis of Time to Mood Event.

	QTP+LI/VAL vs PLA+LI/VAL	
	Study 126	**Study 127**
Hazard Ratio (HR)	0.28	0.32
95% CI for HR	(0.21, 0.38)	(0.24, 0.42)
p-value	<0.001	<0.001

Source: Clinical Study Report D1447C00126, Table 11.2.1-7 (pg 718); Clinical Study Report D1447C00127, Table 11.2.1-7 (pg 699)

Table 9. Sensitivity Analysis: Stratified Log Rank Test

	QTP+LI/VAL vs PLA+LI/VAL	
	Study 126	**Study 127**
Log-Rank Test p-value	<0.001	<0.001

Source: Clinical Study Report D1447C00126, Table 11.2.1-8 (pg 718); Clinical Study Report D1447C00127, Table 11.2.1-8 (pg 700)

3.1.6 REVIEWER'S COMMENTS.

In studies 126 and 127, quetiapine treatment arms (oral tablets 400mg to 800mg daily in divided doses) were statistically superior to corresponding placebo arms with respect to time to mood event when used as adjunct with a mood stabilizer (lithium or valproate). The p-values obtained from Cox-proportional hazard model were < 0.001. The sponsor wants to claim statistical significance of quetiapine on secondary endpoints: time to manic event and time to depressed event. However, the studies were not designed to collect time to first manic event and first depressed event separately. The primary efficacy endpoint (time to mood event) is a composite endpoint, defined as time to manic, depressed or mixed episode, whichever comes first. If a patient has a mood event due to a depressed episode, the time to first manic event would need to be censored on the date of the depressed episode and vice versa. Because of this issue, the results on these individual components as key secondary endpoints are difficult to interpret.

3.2 EVALUATION OF SAFETY

Not evaluated by this reviewer. Please refer to clinical review of this application for a detailed safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

The reviewer conducted the exploratory Cox-proportional hazard analysis of time to mood event for age, gender and origin subgroups. Among all the subgroups, the treatment effect appeared to be numerically in favor of quetiapine when compared with placebo.

Table 10. Summary of the Patients with Mood Event and Censored Patients by Age, Gender and Race Subgroups.

	Study 126		Study 127	
	QTP+LI/VAL	**PLA+LI/VAL**	**QTP+LI/VAL**	**PLA+LI/VAL**
Younger than 40year				
Total number of patients	138 (100%)	162 (100%)	136 (100%)	165 (100%)
Patients who had mood event	23 (16.67%)	72 (44.44%)	27 (19.85%)	82 (49.70%)
40-65 years				
Total number of patients	190 (100%)	194 (100%)	171 (100%)	144 (100%)
Patients who had mood event	38 (20.00%)	102 (52.58%)	35 (20.47%)	79 (54.86%)
Older than 65 years				
Total number of patients	8 (100%)	11 (100%)	3 (100%)	4 (100%)
Patients who had mood event	1 (12.50%)	6 (54.55%)	1 (33.3%)	2 (50.00%)
Male				
Total number of patients	144 (100%)	172 (100%)	151 (100%)	145 (100%)
Patients who had mood event	26 (18.06%)	82 (47.67%)	28 (18.54%)	84 (57.93%)
Female				
Total number of patients	192 (100%)	195 (100%)	159 (100%)	168 (100%)
Patients who had mood event	36 (18.75%)	98 (50.26%)	35 (22.01%)	79 (47.02%)
Caucasian				
Total number of patients	321 (100%)	358 (100%)	248 (100%)	261 (100%)
Patients who had mood event	61 (19.00%)	175 (48.88%)	53 (21.37%)	140 (53.64%)
Other				
Total number of patients	15 (100%)	9 (100%)	62 (100%)	52 (100%)
Patients who had mood event	1 (6.67%)	5 (55.56%)	10 (16.13%)	23 (44.53%)

Source: Reviewer's Results

Table 11. Subgroup Analysis: Cox-proportional Hazard Analysis of Time to Mood Event

	QTP+LI/VAL vs PLA+LI/VAL	
	Study 126	**Study 127**
Younger than 40years		
Hazard Ratio (HR)	0.301	0.335
95% CI for HR	(0.188, 0.482)	(0.217, 0.518)
40-65 years		
Hazard Ratio (HR)	0.260	0.300
95% CI for HR	(0.178, 0.378)	(0.201, 0.447)
Older than 65 years		
Hazard Ratio (HR)	Not many patients	Not many patients
95% CI for HR		
Male		
Hazard Ratio (HR)	0.297	0.252
95% CI for HR	(0.191, 0.462)	(0.164, 0.387)
Female		
Hazard Ratio (HR)	0.266	0.395
95% CI for HR	(0.181, 0.391)	(0.265, 0.589)
Caucasian		
Hazard Ratio (HR)	0.290	0.322
95% CI for HR	(0.217, 0.389)	(0.234, 0.441)
Other		
Hazard Ratio (HR)	Not many patients	0.312
95% CI for HR		(0.148, 0.658)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

The sponsor conducted exploratory subgroup analysis of efficacy by assigned mood stabilizer. In addition, subgroup analysis by region (US, Rest of the World) was conducted in Study 126. Among all the subgroups, the treatment effect appeared to be numerically in favor of quetiapine when compared with placebo.

Table 12. Study 126 Subgroup Analysis by Region: Cox-proportional Hazard Analysis of Time to Mood Event

	QTP+LI/VAL	PLA+LI/VAL	QTP+LI/VAL vs PLA+LI/VAL	
US				
Total number of patients	81 (100%)	92 (100%)	Hazard Ratio (HR)	0.19
Patients who had mood event	11 (13.58%)	47 (51.09%)	95% CI for HR	(0.10, 0.36)
Rest of the World				
Total number of patients	255 (100%)	275 (100%)	Hazard Ratio (HR)	0.31
Patients who had mood event	51 (20.00%)	133 (48.36%)	95% CI for HR	(0.23, 043)

Source: Clinical Study Report D1447C00126, Table 11.2.1-6 (pg 717)
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 13. Summary of the Patients with Mood Event and Censored Patients by Mood Stabilizer

	Study 126		Study 127	
	QTP+LI/VAL	PLA+LI/VAL	QTP+LI/VAL	PLA+LI/VAL
Lithium				
Total number of patients	143 (100%)	153 (100%)	131 (100%)	134 (100%)
Patients who had mood event	25 (17.48%)	75 (49.02%)	35 (26.72%)	70 (52.24%)
Valproate				
Total number of patients	193 (100%)	214 (100%)	179 (100%)	179 (100%)
Patients who had mood event	37 (19.17%)	105 (49.07%)	28 (15.64%)	93 (51.96%)

Source: Clinical Study Report D1447C00126, Table 11.2.1-6 (pg 716), Clinical Study Report D1447C00127, Table 11.2.1-6 (pg 697)

Table 14. Subgroup Analysis by Mood Stabilizer: Cox-proportional Hazard Analysis of Time to Mood Event

	QTP+LI/VAL vs PLA+LI/VAL	
	Study 126	Study 127
Lithium		
Hazard Ratio (HR)	0.25	0.40
95% CI for HR	(0.16, 0.40)	(0.27, 0.61)
Valproate		
Hazard Ratio (HR)	0.30	0.25
95% CI for HR	(0.21, 0.44)	(0.16, 0.38)

Source: Clinical Study Report D1447C00126, Table 11.2.1-6 (pg 716); Clinical Study Report D1447C00127, Table 11.2.1-6 (pg 697)
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

In studies 126 and 127, quetiapine treatment arms (oral tablets 400mg to 800mg daily in divided doses) were statistically superior to corresponding placebo arms with respect to time to mood event when used as adjunct with a mood stabilizer (lithium or valproate). The p-values obtained from Cox-proportional hazard model were < 0.001. The sponsor wants to claim statistical significance of quetiapine on secondary endpoints: time to manic event and time to depressed event. However, the studies were not designed to collect time to first manic event and first depressed event separately. The primary efficacy endpoint (time to mood event) is a composite endpoint, defined as time to manic, depressed or mixed episode, whichever comes first. If a patient has a mood event due to a depressed episode, the time to first manic event would need to be censored on the date of the depressed episode and vice versa. Because of this issue, the results on these individual components as key secondary endpoints are difficult to interpret.

5.2 CONCLUSIONS AND RECOMMENDATIONS

When used as adjunct with a mood stabilizer (lithium or valproate) the quetiapine fumarate treatment arm (oral tablets 400mg to 800mg daily in divided doses) showed positive maintenance effect compared with placebo arm for adult patients with Bipolar I Disorder (as measured by time to mood event).

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/s/

George Kordzakhia
3/5/2008 02:22:22 PM
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Peiling Yang
3/5/2008 02:31:30 PM
BIOMETRICS

James Hung
3/19/2008 09:49:19 AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-639/S-037

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-639 S037
Drug:	Quetiapine IR
Trade Name:	Seroquel
Sponsor:	Astra Zeneca
Indication:	Treatment of Bipolar Disorder
Submission Type:	SE1, SLR
Submission Date:	7/19/07, 10/29/07
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

Background: The sponsor submitted an Efficacy Supplement (SE1-037) and PLR label for Seroquel immediate release (IR) tablets. The review compared the PLR label submitted with supplement 037 by the sponsor with the last approved non-PLR label for Seroquel IR. The last approved non-PLR label used for this comparison was the February, 2008 version.

Reviewer Comments: The content of the clinical pharmacology sections of the PLR label is the same as that of the last (February 08) approved non-PLR label. Under Dosage and Administration: Bipolar Disorder, there is a section on Maintenance which is not in the last (2/08) non-PLR label. However, Seroquel for maintenance treatment of bipolar disorder as adjunct therapy to lithium or divalproex is under review in the Clinical Division. In the HIGHLIGHTS section under Use in Specific Populations: Hepatic Impairment, the lower starting dose should be 25 mg/day not 50 mg/day (See Attached PLR label). The reformatting is acceptable from OCP perspective. The following are the sections compared by the reviewer.

Clinical Pharmacology:
Pharmacodynamics
Pharmacokinetics
Absorption
Distribution
Metabolism and Elimination
Age, Gender, Race, Smoking
Renal Insufficiency
Hepatic Insufficiency
Drug-Drug Interactions

Dosage and Administration:
Dosing in Special Populations

/s/: Kofi A. Kumi, Ph.D.

RD/FT Initialed by Raman Baweja, Ph.D.

NDA 20-639, DPP (HFD-130), DCP1 (Mehta, UppoorR, Baweja, KumiK), CDR (Biopharm.)

48 pages of draft labeling have been withheld as b4 (CCI/TS) immediately following this page

02/08 SIC 30417-04

SEROQUEL
(quetiapine fumarate)
TABLETS

RX ONLY

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen 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 (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SEROQUEL (quetiapine) is not approved for the treatment of patients with Dementia-Related Psychosis.

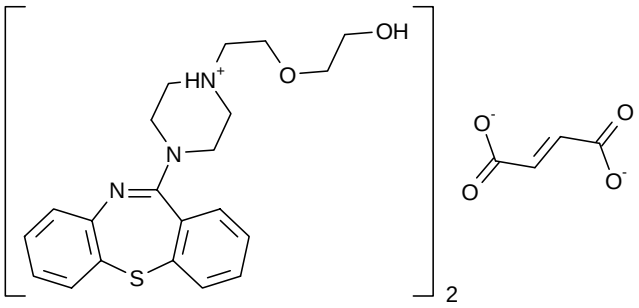
Suicidality and Antidepressant Drugs

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 pediatric patients. (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

DESCRIPTION

SEROQUEL® (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 $C_{42}H_{50}N_6O_4S_2 \bullet C_4H_4O_4$ 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.

CLINICAL PHARMACOLOGY

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 α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

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 α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

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.

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±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}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.

Population Subgroups:

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

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 (Clcr=10-30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (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_{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**).

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 under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

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** under **PRECAUTIONS**).

Clinical Efficacy Data

Bipolar Disorder

Depression

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

The primary rating instrument used to assess depressive symptoms in these studies was the 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).

Mania

The efficacy of SEROQUEL in the treatment of acute 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

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 and 800 mg per day.

Adjunct Therapy

In this 3-week placebo-controlled trial, 170 patients with acute 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 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.

Schizophrenia

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. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

4. In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a tid schedule), 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 to 750 mg/day were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

5. In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

6. In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

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 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

Bipolar Disorder

SEROQUEL is indicated for the treatment of both:

- depressive episodes associated with bipolar disorder
- acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex.

Depression

The efficacy of SEROQUEL was established in two identical 8-week randomized, placebo-controlled double-blind clinical studies that included either bipolar I or II patients (See **CLINICAL PHARMACOLOGY**). Effectiveness has not been systematically evaluated in clinical trials for more than 8 weeks.

Mania

The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania (See **CLINICAL PHARMACOLOGY**). Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy.

The physician who elects to use SEROQUEL for extended periods in bipolar disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

Schizophrenia

SEROQUEL is indicated for the treatment of schizophrenia.

The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

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 2

Age Range	**Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated**

	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
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 health care 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.

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.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. 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.

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 Seroquel (see **ADVERSE REACTIONS**, **Hyperglycemia**). 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 events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

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

PRECAUTIONS

General:

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_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.

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). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (See **DOSAGE AND ADMINISTRATION**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

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/mm^3) should discontinue SEROQUEL and have their WBC followed until recovery (See ADVERSE REACTIONS).

Cataracts: **The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients 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.**

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.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients and levels of 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 divalproate, 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.

Cholesterol and Triglyceride Elevations: In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol ≥240 mg/dL and

triglycerides ≥200 mg/dL were 16% and 23% for SEROQUEL treated patients respectively compared to 7% and 16% for placebo patients respectively. In bipolar depression trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 9% and 14% for SEROQUEL treated patients respectively, compared to 6% and 9% for placebo patients respectively.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see **Carcinogenesis**). 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 contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. 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; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, 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% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, 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 and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with 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% for SEROQUEL and 2% for placebo.

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% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% 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% of patients on SEROQUEL compared to 9% of placebo patients. In bipolar depression trials, somnolence was reported in 28% of patients on SEROQUEL

compared to 7% of placebo patients. In these trials, sedation was reported in 30% of patients on SEROQUEL compared to 8% 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.

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.

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.

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.

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%).

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal Impairment and Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

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 **Orthostatic Hypotension**).

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.

Information for Patients

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

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.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5

day 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 hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

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.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

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.

Laboratory Tests

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 PRECAUTIONS: Leukopenia, neutropenia and agranulocytosis)**

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.

The Effect of Other Drugs on Quetiapine

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) 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**).

Divalproex: Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) 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 bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). 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 bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

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 tid 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 bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant.

Lithium: Concomitant administration of quetiapine (250 mg tid) 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 tid 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.

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^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 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^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 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^2 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-yr 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 Hyperprolactinemia in **PRECAUTIONS, General**).

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^2 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^2 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^2 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^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

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^2 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^2 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^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 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^2 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^2 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^2 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^2 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.

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

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.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established. Anyone considering the use of SEROQUEL in a child or adolescent must balance the potential risks with the clinical need.

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 Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for SEROQUEL consisting of over 3700 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) and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia.

Of these approximately 3700 subjects, approximately 3400 (2300 in schizophrenia, 405 in acute bipolar mania, and 698 in bipolar depression) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 992.6 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 events 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 events without first grouping similar types of events into a smaller number of standardized event categories.

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

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

Adverse Findings Observed in Short-Term, Controlled Trials

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

Bipolar Disorder:

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

Mania: Overall, discontinuations due to adverse events 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.

Schizophrenia: Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events 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 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events 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 2. Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (monotherapy)

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

SGPT Increased	5%	1%
SGOT 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%
Special Senses		
Amblyopia	2%	1%

[1] Events 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 these studies, the most commonly observed adverse events 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 (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%).

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 3-weeks) of acute mania in 5% 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 3. Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy)

Body System/ Preferred Term	SEROQUEL (n=196)	PLACEBO (n=203)
Body as a Whole		
Headache	17%	13%
Asthenia	10%	4%
Abdominal Pain	7%	3%
Back Pain	5%	3%
Cardiovascular		
Postural Hypotension	7%	2%
Digestive		
Dry Mouth	19%	3%
Constipation	10%	5%
Metabolic and Nutritional		
Weight Gain	6%	3%
Nervous		
Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
Respiratory		
Pharyngitis	6%	3%

[1] Events 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, and nausea.

In these studies, the most commonly observed adverse events 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 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 8-weeks) of bipolar depression in 5% 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 4. Treatment-Emergent Adverse Experience Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression

Body System/ Preferred Term	SEROQUEL (n=698)	PLACEBO (n=347)
Gastrointestinal Disorders		
Dry Mouth	44%	13%
Constipation	10%	4%
Dyspepsia	7%	4%
Vomiting	5%	4%
General Disorders and Administrative Site Conditions		
Fatigue	10%	8%
Metabolism and Nutrition Disorders		
Increased Appetite	5%	3%
Nervous System Disorders		
Sedation	30%	8%
Somnolence	28%	7%
Dizziness	18%	7%
Lethargy	5%	2%
Respiratory, Thoracic, and Mediastinal Disorders		
Nasal Congestion	5%	3%

[1] Events 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, and headache.

In these studies, the most commonly observed adverse events 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 dry mouth (44%), sedation (30%), somnolence (28%), dizziness (18%), constipation (10%), lethargy (5%), and nasal congestion (5%).

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

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

Dose-related Adverse Events: Spontaneously elicited adverse event 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 events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

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.

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.

SEROQUEL

Dose Groups	Placebo	75 mg	150 mg	300 mg	600 mg	750 mg
Parkinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS incidence	16%	6%	6%	4%	8%	6%
Anticholinergic medications	14%	11%	10%	8%	12%	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 events 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 events (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.

Vital Signs and Laboratory Studies

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% compared to 2% for placebo.

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

In placebo controlled monotherapy clinical trials involving 3368 patients on SEROQUEL 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 SEROQUEL, compared to 0.1% (2/1349) in patients treated with placebo. **(See PRECAUTIONS: Leukopenia, neutropenia and agranulocytosis)**

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

Hyperglycemia

In 2 long-term placebo-controlled clinical trials, mean exposure 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dl) for patients more than 8 hours since a meal was 18.0 per 100 patient years for SEROQUEL (10.7% of patients) and 9.5 for placebo per 100 patient years (4.6% of patients).

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 patients treated with SEROQUEL and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl was 3.5% for quetiapine and 2.1% for placebo.

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 ≥200 mg/dl was 1.7% and the incidence of a fasting treatment-emergent blood glucose level ≥ 126mg/dl was 2.6%.

ECG Changes: 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 may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported events are included except those already listed in Table 2 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be

uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events 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 events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Nervous System: ***Frequent:*** hypertonia, dysarthria; ***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: ***Frequent:*** palpitation; ***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:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation.

Metabolic and Nutritional System: ***Frequent:*** peripheral edema; ***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: ***Frequent:*** sweating; ***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: ***Frequent:*** leukopenia; ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia.

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

Post Marketing Experience:

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: 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.

OVERDOSAGE

Human experience: In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (**See PRECAUTIONS: Orthostatic Hypotension**). 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.

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.

DOSAGE AND ADMINISTRATION

Bipolar Disorder

Depression

Usual Dose: 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 the 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.

Mania

Usual Dose: When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL should be initiated in bid 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 bid 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 indicates that the majority of patients responded between 400 to 800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Schizophrenia

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. 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 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 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 300mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

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**). 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 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

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

Maintenance Treatment: 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.

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.

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 reevaluated periodically.

HOW SUPPLIED

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 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [See USP].

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^2 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^2 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^2 basis.

Medication Guide
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**
• all risks and benefits of treatment with antidepressant medicines
• all treatment choices for depression or other serious mental illness

What is the most important information I should know about 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) 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 a 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 takes. 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.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

SEROQUEL is a trademark of the AstraZeneca group of companies

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AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
Made in USA
Rev. 02/08 SIC 30417-04

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

/s/

Kofi Kumi
3/4/2008 01:36:02 PM
BIOPHARMACEUTICS

Raman Baweja
3/4/2008 03:24:12 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-639/S-037

OTHER REVIEW(S)

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: February 6, 2008

TO: Doris Bates, Ph.D., Regulatory Project Manager
Earl Hearst, M.D., Medical Officer

FROM: Dianne Tesch, Consumer Safety Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA or IND: #20-639/037

APPLICANT: AstraZeneca

DRUG: quetiapine fumarate

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Maintenance treatment of Bipolar I Disorder

CONSULTATION REQUEST DATE: September 20, 2007

DIVISION ACTION GOAL DATE: February 19, 2008

PDUFA DATE: May 19, 2008

I. BACKGROUND:

Bipolar I Disorder is a psychiatric disorder that is characterized by one or more manic or mixed episodes, usually accompanied by major depressed episodes. It is a serious, lifelong medical condition, which is associated with a lifetime risk of suicide attempt up to 50%. The prevalence of bipolar disorder is estimated to be 1 to 3.5%, evenly distributed between men and women. It is estimated that only 60% of those suffering from a bipolar disorder receive appropriate pharmacotherapy.

Current therapies for bipolar disorder prevent recurrence of illness in only 25 to 33% of patients. While some patients can be safely treated with a single medication, the majority of patients require multiple medications to manage the numerous symptoms of bipolar disorder.

Typically, mood stabilizers are used to induce remission in patients with acute mania or hypomania. Lithium and certain anticonvulsants, especially valproate, carbamazepine, oxcarbazepine, and lamotrigine, act as mood stabilizers and are similarly effective. Quetiapine fumarate was first approved by the FDA in 1997 for the treatment of patients with schizophrenia. The efficacy and safety of quetiapine when used as monotherapy and as adjunct to mood stabilizers (lithium and divalproex) in the treatment of bipolar mania have been shown in a series of randomized placebo-controlled studies.

Previous studies of quetiapine in the treatment of mania examined efficacy during the acute and continuation phases of the illness, but not during the maintenance phase, when patients have achieved symptomatic remission but are still at risk for recurrence. For this reason, the pivotal study in support of this NDA examined the efficacy, safety and tolerability of quetiapine as adjunct to lithium or divalproex in preventing subsequent mood episodes.

The primary objective was to increase time to recurrence of a manic event, defined as:

1. initiation of an antipsychotic, mood stabilizer other than the assigned mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a manic or mixed event,
2. hospitalization for a manic or mixed event,
3. Young Mania Rating Scale score .20 at 2 consecutive assessments or at the final assessment if the patient discontinues, or
4. discontinuation from the study by the patient if, in the opinion of the investigator, the discontinuation was due to a manic or mixed event.

The primary efficacy measure was the Young Mania Rating Scale (YMRS)

The secondary efficacy measures were the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impression-Bipolar (CGI-BP; Spearing et al 1997), and the Life Charting Method Self/Prospective Rating (NIMH-LCM S/P, the Positive and Negative Syndrome Scale- Positive Subscale (PANSS-P), the Sheehan Disability Scale (SDS), and the Psychological General Well-being Scale (PGWB).

Safety and tolerability were assessed by laboratory values, vital signs, physical examinations, electrocardiograms, and evidence of extrapyramidal symptoms (EPS) assessed by the following rating scales: Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS).

All patients were to be treated with quetiapine and the assigned mood stabilizer for at least 20 weeks up to 36 weeks before they can be randomized. The study consisted of enrollment and 2 phases, the Open-label treatment phase and the Randomized Treatment Phase.

There were no special concerns at any of the sites for this application. The sites were chosen for inspection because they were high enrollers.

Protocol:
#D1447C00127 A Multicenter, Randomized, Parallel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (oral tablets 400 mg to 800 mg daily in divided doses) to Placebo When Used as Adjunct to Mood Stabilizers (Lithium or Divalproex) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor City, State or Country	**Indication: Protocol #: and # of Subjects:**	**Insp. Date**	**Final Classification**
CI #1 Dr. Azfar Malik St. Louis, MO	#D1447C00127 28 subjects	11/26/07- 12/5/07	NAI

Name of CI, IRB, or Sponsor City, State or Country	**Indication: Protocol #: and # of Subjects:**	**Insp. Date**	**Final Classification**
CI #2 Dr. Dwight St. Clair Wichita, KS	#D1447C00127 26 subjects	11/26/07- 12/7/07	NAI
IRB	N/A		
SPONSOR	N/A		

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-R = Response Requested = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. **Name of CI**

   Dr. Azfar Malik
   Psych Care Consultants Research
   5000 Cedar Plaza Parkway
   Suite 350
   St. Louis, MO 63128

   a. **What was inspected**: At this site, sixty-nine subjects were screened; There were thirteen screen failures. Fifty-six subjects were enrolled, twenty-eight were randomized, and nine subjects completed the study. There was one death unrelated to the protocol. There were eleven SAEs for seven subjects. An in depth audit of all subjects' records was conducted.

   b. **General observations/commentary**: There were no regulatory violations at this site.

   c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Dr. Dwight St. Clair
   Heartland Research Associates
   1709 South Rock Rd.
   Wichita, KS 67207

   a. **What was inspected**: At this site, forty subjects were screened; thirty-four subjects were entered into the open-label phase, and twenty-six were randomized. No subjects completed the study due to study closure by the sponsor. There were no deaths. An in depth audit of seventeen subjects' records was conducted.

   b. **General observations/commentary**: No regulatory violations were noted.

   c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This PDUFA inspection audited two study sites. No significant regulatory violations were noted. The data from these sites are considered acceptable for the proposed indication.

{See appended electronic signature page}

Dianne Tesch, Consumer Safety Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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/s/

Dianne Tesch
2/8/2008 12:19:35 PM
CSO

Tejashri Purohit-Sheth
2/8/2008 01:15:27 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-639/S-037

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

Doctype	Number	Supp. Type	Supp. No.	Proprietary Name Generic Name	Dosage Form & Strengths
NDA #	20639	SE1	037	Seroquel (quetiapine fumarate)	Tablets 25, 50, 100, 200, 300, 400 mg

Applicant: AstraZeneca Pharmaceuticals LP

Approval Date, If Known PDUFA Goal Date is May 19, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☑ NO ☐

b) If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) SE1 for new indication.

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES☑ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☑ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

THREE

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☑

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

The requested studies have not yet been submitted. A Pediatric Exclusivity Determination will be made after these studies are received.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☑

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☑ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #	20-639	Seroquel (quetiapine fumarate)	Tablets 25, 50, 100, 200, 300, 400 mg
NDA #	22-047	Seroquel XR (quetiapine fumarate)	Extended Release Tablets, 50, 200, 300, 400 mg

2. Combination product. ***Not Applicable.***

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☑ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the

application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES☑ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☑ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☑

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☑

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation 1: Study D1447C00126

Investigation 2: Study D1447C00127.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☑
Investigation #2	YES ☐	NO ☑
Investigation #3	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☑
Investigation #2	YES ☐	NO ☑
Investigation #3	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any

that are not "new"):

Investigation 1: Study D1447C00126
Investigation 2: Study D1447C00127.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 Study D1447C00126!
IND #32132 YES ☑ ! NO ☐
! Explain:

Investigation #2 Study D1447C00127!
!
IND # 32132 YES ☐ ! NO ☐
! Explain:

Investigation #3 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

NOT APPLICABLE

Investigation #1 !

YES ☐	NO ☐
Explain:	Explain:

Investigation #2	
YES ☐	NO ☐
Explain:	Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☑

If yes, explain:

==========

Name of person completing form: Doris J. Bates, Ph.D.
Title: Regulatory Health Project Manager
Date: April 13, 2008

Name of Office/Division Director signing form: Thomas P. Laughren, M.D.
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Doris Bates
5/13/2008 10:25:00 AM

Thomas Laughren
5/13/2008 10:50:27 AM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 20-639 Supplement Number: 037 NDA Supplement Type (e.g. SE5): SE1

Division Name: Division of Psychiatry Products, HFD-130

Stamp Date: 19JUL2007 PDUFA Goal Date: 19MAY2008

Proprietary Name: Seroquel Established/Generic Name: quetiapine fumarate

Dosage Form: Tablets Applicant/Sponsor: AstraZeneca Pharmaceuticals LP

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1)Schizophrenia
(2) Monotherapy treatment of acute manic episodes associated with bipolar disorder
(3) Adjunctive therapy with lithium or divalproex in treatment of acute manic episodes associated with bipolar disorder
(4) Major depressive episodes associated with bipolar disorder

Q1: Is this application in response to a PREA PMC? Yes ☐ Continue

No **XX** Please proceed to Question 2.

If Yes, NDA/BLA#: Supplement #: PMC #:

Does the division agree that this is a complete response to the PMC?

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s); **XX** indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): **1**
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Maintenance treatment of bipolar I disorder [manic, mixed, or depressed episodes] as adjunct therapy to lithium or divalproex.

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

XX No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

XX No: Please check all that apply:

XX Partial Waiver for selected pediatric subpopulations (Complete Sections B)

XX Deferred for the remaining pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible #	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
XX	Neonate	0 wk. __ mo.	__ wk. 12 mo.	XX	☐	☐	☐
XX	Other	1 yr. __ mo.	9 yr. __mo.	XX	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? **XX** No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? **XX** No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

XX Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

XX Other (e.g., patients geographically dispersed):

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

XX Justification: ***Presently, it is not possible to diagnose bipolar disorder reliably in the above listed pediatric age groups. Therefore, appropriate studies cannot be developed and carried out.***

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
XX	Other	10 yr. __ mo.	17 yr. __ mo.	☐	☐	XX	XX[1]	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): June 1, 2015 [1]Deferral certification noted above = the fact that deferral had been requested by and granted to the firm for this indication in January, 2007, prior to the enactment of FDAAA.							

Are the indicated age ranges (above) based on weight (kg)? XX No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? XX No; ☐ Yes.

* Other Reason: pediatric studies should be delayed until additional safety or effectiveness data have been collected. We are aware that submission of pediatric studies under your existing Written Request is imminent, and these studies, once reviewed, may be sufficient to address the PREA requirement for this indication.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 4/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

Doris Bates
5/13/2008 10:26:43 AM

NDA REGULATORY FILING CHECKLIST

NDA # 20639 Efficacy Supplement Type SE- SE1 Supplement # 037

Proprietary Name, Established Name: Seroquel (quetiapine fumarate) Tablets
Dosage Form, Strengths: Tablets, 20, 50, 100, 150, 200, 300, 400 mg
Indication(s) requested: **use of quetiapine as adjunctive therapy with lithium or divalproex mood stabilizers in the maintenance treatment of bipolar I disorder.**

Applicant: AstraZeneca UK, Ltd.
Agent for Applicant (if applicable): AstraZeneca Pharmaceuticals LP

Date of Application: 19JUL07 Date of Receipt: 19JUL07 Clock started: 19JUL07
Filing Meeting: 12SEP07 Filing Date: 17SEP07 Day 74: 01OCT07
User Fee Goal Date: 19MAY08
List referenced IND numbers:

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND 32,132; IND 45,456; IND 73,864; DMFs (b) (4)

FORM FDA 356h (10/05) Recreated by Regulatory Affairs, AstraZeneca Pharmaceuticals PAGE 1

Type of Original NDA:	**(b)(1)**	**X**		(b)(2)	☐
AND (if applicable)					
Type of Supplement:	**(b)(1)**	**X**		(b)(2)	☐

Review Classification: **S**	**X**	P		☐
Resubmission after withdrawal?	☐	Resubmission after RTF?		☐
Chemical Classification: (1,2,3 etc.)	**3**	Other (orphan, OTC, etc.)		

Form 3397 (User Fee Cover Sheet) submitted:	**YES**	**X**	NO	☐
User Fee Status: **Paid** **X**	Exempt (orphan, government)	☐	Waived (e.g., small business, public health)	☐
Is the application affected by the Application Integrity Policy (AIP)?	YES	☐	**NO**	**X**
If yes, explain:				
If yes, has OC/DMPQ been notified of the submission?			***not applicable***	
Does the submission contain an accurate comprehensive index?	YES	**X**	NO	☐
Was form 356h included with an authorized signature for the submission?	YES	**X**	NO	☐
Is the submission complete as required under 21 CFR 314.50?	YES	**X**	NO	☐

Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐ NO ☐
2. **This application is an eNDA or combined paper + eNDA** **YES** ☐ **NO** ☐
   - **This application is:** **All electronic X** **Combined paper + eNDA** ☐
   - **This application is in:** **NDA format** ☐ **CTD format** ☐ **Combined NDA / CTD formats X**

Does the eNDA follow the guidance? YES X NO ☐
(http://www.fda.gov/cder/guidance/2353fnl.pdf)

If combined paper + eNDA, which parts of the application were submitted in electronic format?
The supplement (submitted via the electronic gateway) consists of the pertinent Module 1 components, the Clinical Overview and Summaries of Clinical Safety and Clinical Efficacy in Module 2, plus two full clinical trial reports within Module 5. Since there was no new information to be included in the CMC (chemistry, manufacturing, and control),

preclinical, or pharmacokinetic sections of this sNDA, Modules 2.3 (Quality Overall Summary), 2.4 (Nonclinical Overview), 2.6 (Nonclinical Summary), 2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods), 2.7.2 (Summary of Clinical Pharmacology Studies), 3 (Quality), and 4 (Nonclinical Study Reports) are cross-referenced to NDA 20-639 and associated supplements.

Additional comments:

3. This application is an eCTD NDA. YES ☐ NO ☐

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

Patent information submitted on form FDA 3542a? YES **X** NO ☐

Exclusivity requested? **YES,** ***three*** Years NO ☐

NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

5-year or 3-year exclusivity ***on the active moiety*** in any approved (b)(1) or (b)(2) application? YES **patent to Sep 26 2011 excl. to Oct 20 2009** NO ☐

Does another drug have orphan drug exclusivity for the same indication? YES ☐ **NO** **X**

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***not applicable***

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

If yes, explain:

Correctly worded Debarment Certification included with authorized signature? **YES** **X** NO ☐

Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?

YES ☐ NO **X**:

Previously required pediatric studies are pending submission separately and should be submitted on or before February 11, 2010.

If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)?

YES **X** NO ☐

Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO **X**

If yes, contact PMHS

Financial Disclosure forms included with authorized signature? YES **X** NO ☐

(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

Field Copy Certification (that it is a true copy of the CMC technical section) ***not applicable***

PDUFA Goal dates correct in tracking system? YES **X** NO ☐

Drug name and applicant name correct in COMIS? YES **X** NO ☐ If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

End-of-Phase 2 Meeting(s)?	Date(s)	**June 2003**			
Pre-NDA Meeting(s)?	Date(s)	**October 2006.**		NO	☐
Any SPA agreements?	Date(s)	YES ☐		NO	X

Project Management

Was electronic Content of Labeling submitted in SPL format? If no, request in 74-day letter.		YES	**X**	NO	☐
Was the PI submitted in PLR format?		YES	**X**	NO	☐
Note: This is the first PLR format submission of labeling for Seroquel IR. Seroquel SR labeling is in PLR format.					
All labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC?		YES	☐	NO	**X**
If Rx, trade name (and all labeling) consulted to OSE/DMETS?		YES	☐	NO	**X**
If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?	**N/A** **X**	YES	☐	NO	☐
Risk Management Plan consulted to OSE/IO?	**N/A** **X**	YES	☐	NO	☐
If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted?	**NA** **X**	YES	☐	NO	☐

Clinical

If a controlled substance, has a consult been sent to the Controlled Substance Staff?		YES	***not applicable*** ☐	NO	☐

Chemistry

Did applicant request categorical exclusion for environmental assessment?		YES	**X**	NO	☐
Establishment Evaluation Request (EER) submitted to DMPQ?	**N/A**	YES	☐	NO	**X**
If a parenteral product, consulted to Microbiology Team?		YES	☐	NO	☐

Additional Comments

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

/s/

Doris Bates
5/13/2008 10:32:52 AM
CSO

MINUTES: FILING MEETING
NDA 20-639 / SE1-037
AstraZeneca: Seroquel (quetiapine) Tablets, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300, 400 mg
SE1-037: maintenance tx. of bipolar disorder as adjunctive therapy w. Li or valproate

Date/Time/Place: Wednesday, September 12, 2007: 2:00 - 3:00 P.M.; WO 22 Rm 4270
Participants: see below.

Reviewer Roster:

Discipline	**Team Leader /Reviewer**
Division Director:	Laughren
Clinical Team Leader II	Khin
Regulatory Project Management:	Bates
Deputy Director/Clinical Reviewer	Mathis/Cai
Clinical Safety:	---
Controlled Substances:	---
DDRE:	---
Statistical:	Chen/Kordzakhia
Nonclinical Pharmacology:	---
Statistical Nonclin Pharmacology:	---
Clinical Pharmacology:	---
Chemistry:	Chidambaram / Pinto
Environmental Assessment (if needed):	---
Microbiology, sterility:	---
Microbiology, clinical (for antimicrobial products only):	---
DSI:	Tesch
DDMAC:	---

Other Consults:

505(b)(2)? No

LETTER DATE: July 19, 2007	STAMP DATE: July 19, 2007
FILING DATE:	September 17, 2007
74-DAY LETTER ISSUE DATE:	October 1, 2007
DATE OF MIDCYCLE MEETING:	~Dec. 19, 2007
DATE OF MONTH 8 MEETING	~March 19, 2008

PDUFA GOALDATE: MAY 19, 2008

ACTION LETTER SIGNATORY AUTHORITY: Division Director or Office Director

DATE REVIEWS ARE DUE:

To Team Leaders:	March 4, 2008
To Clinical Team Leader:	March 19, 2008
To Division Director:	April 26, 2008

Version: 12/15/2004
This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the View' tab; drag the cursor down to 'Toolbars'; click on Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

sNDA Filing Minutes
NDA 20-639 / SE1-037

Background: SE1-037 provides for the use of quetiapine as maintenance therapy in the adjunctive treatment of bipolar disorder, manic or mixed, with lithium or valproate.

The initial approvals of quetiapine for the acute treatment of bipolar disorder, manic or mixed, as monotherapy [S-016] and as adjunctive therapy [S-017] were granted on January 12, 2004 without Phase 4 commitments other than pediatric. The pediatric commitment was due on February 11, 2008 under both PREA and Pediatric Exclusivity [Written Request]. On February 3, 2005, this due date was extended to February 11, 2010 in an amendment to the WR.

Meeting Details:

Per reviewers, are all parts in English or English translation? YES X NO

CLINICAL FILE X REFUSE TO FILE
- Clinical site inspection needed? YES X NO
- Domestic or foreign? Domestic X Foreign
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- Is application affected by AIP N/A X YES NO
- Has Division made a recommendation regarding exception to the AIP to permit review based on medical necessity or public health significance? N/A X YES NO
- Summarize Clinical Issues. see 74-day letter.
- Clinical Questions for 74-Day Letter? N/A ***YES*** NO

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE

STATISTICS N/A FILE X REFUSE TO FILE
- Questions for 74-Day Letter? ***YES***

CLINICAL PHARMACOLOGY N/A FILE X REFUSE TO FILE
- Biopharm. inspection needed? YES NO X
- Domestic or foreign? Domestic | | Foreign |
- Questions for 74-Day Letter? No - OCP will compare PLR to pre-PLR labeling for OCP sections.

NONCLINICAL PHARMACOLOGY N/A X FILE REFUSE TO FILE
- GLP inspection needed? YES NO
- Carc Studies? YES NO
- Date of CAC

CHEMISTRY N/A FILE X REFUSE TO FILE
- Establishment(s) ready for inspection? YES NO
- Microbiology consult needed? YES NO
- Other expert consult needed? EA, FONSI

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

The application is unsuitable for filing. See attached summary of deficiencies.

X The application, on its face, appears to be sufficiently well-organized and indexed to permit filing. This decision does not guarantee that no deficiencies will be identified during review. It also does not guarantee a first cycle approval action.

No filing issues identified.

X Filing issues to be communicated by Day 74 (see above for date due to RPM).

ACTION ITEMS: [delete those that do not apply]

74-day letter to be sent with filing review issues [clinical, statistical]

COMMENTS:

Doris J. Bates, Ph.D.
Regulatory Project Manager, HFD-130

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/s/

Doris Bates
5/13/2008 10:30:44 AM

NDA 20-639 S-037
ACTION PACKAGE CHECKLIST -- SUPPLEMENTAL NDA

Application Information			
NDA 20-639	Efficacy Supplement Type SE1	Supplement Number 037	
Drug: Seroquel (quetiapine fumarate) Tablets		Applicant: AstraZeneca Pharmaceuticals, LP	
RPM: Bates		HFD-130	Phone # 301 796 1040

Application Type: **(✓)** 505(b)(1) **( )** 505(b)(2)
(This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

❖ Application Classifications:	
• Review priority	**(✓)** Standard **( )** Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	***Pediatric (WR and PREA)***
❖ User Fee Goal Dates	May 19, 2008
❖ Special programs (indicate all that apply)	**(✓)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(✓)** Paid UF ID number _PD3007087___
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) _____
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify) _____
❖ Application Integrity Policy (AIP) *NOT APPLICABLE*	
• Applicant is on the AIP	**( )** Yes **( )** No
• This application is on the AIP	**( )** Yes **( )** No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(✓)** Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**(✓)** Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	patent on active moiety until 06SEP2011 exclusivity until 20OCT2009
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	**( )** Yes, Application #_____ **(✓)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	See Table of Contents
General Information	
❖ Actions	
• Proposed action	**(✓)** AP **( )** TA **( )** AE **( )** NA
• Previous actions (specify type and date for each action taken)	none - first cycle approval
• Status of advertising (approvals only)	**(✓)** Materials requested in AP letter **( )** Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(✓)** Yes **( )** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(✓) TBD by Press Office** **( )** None **( )** Press Release **( )** Talk Paper **( )** Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	✓
• Most recent applicant-proposed labeling	✓
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	✓ See Clinical and Clinical Pharmacology reviews
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	NOT APPLICABLE
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	See AP letter for all information
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	June 4, 2003
• Pre-NDA meeting (indicate date)	January 10, 2007
• Pre-Approval Safety Conference (indicate date; approvals only)	---

• Other	October 15, 2003 June 5, 2006 January 14, 2005
❖ Advisory Committee Meeting	NOT APPLICABLE
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NOT APPLICABLE
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader)	✓
Clinical Information	
❖ Clinical review(s)	✓
❖ Microbiology (efficacy) review(s)	NA
❖ Safety Update review(s)	NA
❖ Risk Management Plan review(s)	NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	✓
❖ Demographic Worksheet *(NME approvals only)*	NA
❖ Statistical review(s)	✓
❖ Biopharmaceutical review(s)	✓ [labeling]
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	✓
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s)	✓: See Memo
❖ Environmental Assessment	
• Categorical Exclusion	✓: See Memo
• Review & FONSI	
• Review & Environmental Impact Statement	
❖ Facilities inspection (provide EER report)	**NOT APPLICABLE** Date completed: **( )** Acceptable **( )** Withhold recommendation
❖ Methods validation	**NOT APPLICABLE** **( )** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews	NA
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	NA

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/s/

Doris Bates

5/13/2008 10:29:13 AM

Bates, Doris J

From: Bates, Doris J
Sent: Thursday, January 24, 2008 12:24 PM
To: 'Patterson, Pat'
Cc: 'Limp, Gerald L'; Hearst, Earl D; Bates, Doris J
Subject: NDA 20-639, S-037: Clinical Review Questions.
Importance: High

Dear Ms. Patterson and Mr. Limp:

Our clinical reviewer has the following questions pertaining to your supplemental NDA. Please respond by reply email, using the 'reply to all' option, to assure immediate delivery of the information to our reviewer. If the information requested below is included in your submission, please indicate where it may be found. Any information provided that is not in the submission should be incorporated by amending the SNDA, but this can be done after an email is sent to us.

*****
Please refer to Seroquel Bipolar Maintenance studies D1447C00126 and 127. Per protocol, patients "began or continued" on open label lithium/valproate and quetiapine after meeting all inclusion/exclusion criteria for entering the open label treatment phase. We have the following questions:

1. How many patients were already taking lithium and valproate when they entered the open label phase? How many patients in each study were started on lithium or valproate at the same time quetiapine was started? What is the rationale for starting both medications [mood stabilizer (Li or valproate) and quetiapine] at the same time?

2. Of the randomized patients in each study, what was the mean number of weeks they were stabilized at the time of randomization?

3. We note that patients could be having either a manic, mixed, or depressive episode at time of study entry. How many patients fell into each of these three categories at study start?

*****
If you have any questions, please feel free to contact us via reply email.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
1/24/2008 12:45:17 PM
CSO
See email for time of transmittal to firm.

Bates, Doris J

From: Bates, Doris J
Sent: Thursday, December 27, 2007 12:33 PM
To: 'Patterson, Pat'
Cc: Hearst, Earl D; Bates, Doris J
Subject: NDA 20-639 S-037

Importance: High

Good afternoon Ms. Patterson:

I have the following question from our clinical reviewer with reference to the above cited supplemental NDA.

> Did you include a methodology for the literature search and a statement of interpretation? If so, please indicate where the information may be found. If not, please provide this information as soon as possible.

I will be out of the office for several days; please use the 'reply to all' option if responding by email. This will assure that our reviewer receives your response immediately, whether or not I am available. Any additional information provided in response to this question should also be submitted directly to the sNDA as an amendment.

Thank you very much,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
12/27/2007 12:37:23 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**SUPPLEMENTAL NDA ACKNOWLEDGED/FILED:
FILING REVIEW ISSUES IDENTIFIED
(CLINICAL / STATISTICAL)**

NDA 20-639 / S-037

Gerald Limp
Director, Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp:

Please refer to your supplemental new drug application (sNDA), referenced above, which was submitted and received on July 19, 2007 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) Tablets.

This supplemental application provides for the use of quetiapine as adjunctive therapy with lithium or valproate in the maintenance treatment of Bipolar I Disorder.

We have completed our filing review for this supplemental application and have determined that your application is sufficiently complete to permit a substantive review. This application has been filed on September 12, 2007 under section 505(b) of the Act and in accordance with 21 CFR 314.101(a). The

In our filing review, we have identified the following review issues:

Clinical

Please submit the following information:

- Provide a table of Principal Investigators which includes their addresses, Center #, and Number of subjects recruited for each center for each study, not counting the sub-investigators.
- Provide the time period and the database(s) covered for the literature review. The individual(s) responsible for this review, the conclusions drawn from it, and a warrant for its accuracy and conclusion should be included.
- With respect to person-year exposure: Please provide the exposure over the whole study period, not just the open-label period.
- Provide demographic analyses of efficacy.
- Provide demographic analysis of common adverse-event reporting rates of randomized period by comparing the drug : placebo odds ratios between demographic subgroups using Breslow-Day Chi-Square test.

Statistical

- For randomized trials D144C00126 and D144C00127, please submit
  (a) SAS programs that produced all efficacy results pertaining to the primary endpoint,
  (b) SAS programs by which the derived variables were produced from the raw variables,
  (c) a list of IND and serial submission numbers of all protocols, amendments, SAPs, and related meetings.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Please also note that our filing review is only a preliminary evaluation of the application, and is not indicative of all deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the partial waiver [ages 0 - < 12 years] and the partial deferral [ages 12 to 16 years] granted on January 12, 2007, for the pediatric study requirement for this application.

Finally, we note that this submission provides the first conversion of your package insert to the PLR Content and Format Requirements. Our Study Endpoints and Label Development (SEALD) Team have created (attached) a list of the most frequently encountered PLR format/content deficiencies. We are asking you to review your submitted PLR labeling to verify that none of these deficiencies are in the PLR labeling submitted on July 19, 2007. If you find that there are deficiencies in the PLR labeling, please amend your application with revised labeling to correct these deficiencies. Additionally, please note that this is not an exhaustive list and you are also encouraged to review our PLR guidance documents located at the following internet address: http://www.fda.gov/cder/regulatory/physLabel/default.htm. We request that you complete this PLR labeling review and respond to us with any necessary revisions to labeling within 30 days of receipt of this letter. We consider this a separate request from the filing review issues listed in this letter, and it may be addressed separately.

If you have any questions, please contact Doris J. Bates, Regulatory Project Manager, by phone at (301) 796-2260 or via secure electronic mail at doris.bates@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

attachment: Common Proposed Labeling Deficiencies

Common Proposed Labeling Deficiencies
Identify and Correct before Labeling Content Review Begins

Highlights:

• Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI.
[See 21 CFR 201.57(d)(6) and Implementation Guidance]

• The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

• The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product].
[See 21 CFR 201.57(a)(1)]

• The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]

• The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).

• For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].

• The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

"(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

• Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).

• A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting.
[See 21 CFR 201.57 (a)(11)].

• Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights.
[See comment #34 Preamble]

• The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]

• A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at

the time of submission and will be edited to the month/year of application or supplement approval.
• A horizontal line must separate the Highlights, Contents, and FPI.
[See 21 CFR 201.57(d)(2)]

Contents:
• The wording of the headings and sub-headings used in the Contents must match the headings and sub-headings used in the FPI. [See 21 CFR 201.57(b)]
• The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
• Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous as the title for a subsection heading.
• Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
• When a subsection is omitted, the numbering does not change.
[See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

8.1 Pregnancy
8.3 Nursing Mothers (not 8.2)
8.4 Pediatric Use (not 8.3)
8.5 Geriatric Use (not 8.4)

• When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI):
• Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
• Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.
• Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at hhtp://www.fda.gov/cder/guidance.
• The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print.
[See Implementation Guidance]
• Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
• Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but

rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
• The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
• There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
• The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
• Regarding information at the end of the labeling, company website addresses are not encouraged. Delete from package insert labeling. The same applies to PPI and MG.
• If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
• Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.
• Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Created: J. Delasko, SEALD Team, 1/29/07
Revised: R. Anderson, SEALD Team, 3/1/07

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/s/

Thomas Laughren
9/24/2007 11:38:26 AM