CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-639/S-016 & S-017

Trade Name: Seroquel Tablets

Generic Name: quetiapine fumarate

Sponsor: AstraZeneca Pharmaceuticals

Approval Date: 01/12/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-639/S-016 & S-017

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	X
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
EA/FONSI	X
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative and Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-639/S-016 & S-017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-639 /S-016, S-017

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

Dear Mr. Limp:

Please refer to your supplemental new drug applications dated December 30, 2002, received December 30, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel® (quetiapine fumarate) Tablets.

We also acknowledge receipt of your submissions dated November 11, and December 23, 2003.

Your submission of November 11, 2003 constituted a complete response to our October 27, 2003 action letter.

These supplemental new drug applications provide for the use of Seroquel® (quetiapine fumarate) tablets:

- As monotherapy in the treatment of acute manic episodes associated with Bipolar I disorder (S-016), and
- As adjunctive therapy with mood stabilizers (lithium or divalproex) in the treatment of acute manic episodes associated with Bipolar I disorder (S-017).

We completed our review of these applications, as amended, and they are approved effective on the date of this letter for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements

NDA 20-639/S-016, S-017." Approval of these submissions by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. 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:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Pediatric Post Marketing Commitment

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 are waiving the pediatric study requirement for neonates through 9 years of age and deferring pediatric studies for ages 10 to 17 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric studies under PREA for use as monotherapy and adjunct therapy for the short-term treatment of acute manic episodes associated with Bipolar I Disorder in pediatric patients ages 10 to 17.

   Final Report Submission: February 11, 2008

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "Required Pediatric Study Commitments".

Please refer to the Agency's Formal Written Request letter (b)(4)----------which the details of your pediatric development program were discussed for Seroquel™.

Superceded "Changes Being Effected" Labeling Supplements

Finally, we have reviewed the content of the following supplemental applications and note that the changes provided for have either been incorporated into the enclosed labeling text or have been further revised and incorporated into the enclosed labeling text. Therefore, these supplemental applications have been superceded and will be retained in our files with no further action.

	Dated:	Received:
S-018	June 13, 1986	July 21, 1987

This "Changes Being Effected" supplemental application provides for revision of the WARNINGS: Neuroleptic Malignant Syndrome (NMS) subsection and OVERDOSAGE section of labeling.

S-019	January 12, 1987	February 2, 1989

This "Changes Being Effected" supplemental application provides for the addition of a subsection in the WARNINGS section of labeling entitled "Hyperglycemia and Diabetes Mellitus".

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, call Dr. Doris Bates, Regulatory Project Manager, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Text for Package Insert

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

/s/

Russell Katz
1/12/04 10:28:48 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-639/S-016 & S-017

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-639/S-016, S-017

AstraZeneca Pharmaceuticals
Attn: Gerald L. Limp
Director, Regulatory Affairs
1800 Concord Pike / PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp:

Please refer to your supplemental new drug applications dated December 30, 2002, received December 30, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel® (quetiapine) Tablets.

We also acknowledge receipt of your submissions dated January 16, 2003, March 17, 2003, March 24, 2003, and September 3, 2003.

These supplemental new drug applications provide for the use of Seroquel (quetiapine) tablets:

- As monotherapy in the treatment of acute manic episodes associated with Bipolar I Disorder (S-016)
- As adjunctive therapy with mood stabilizers (lithium or divalproex) in the treatment of acute manic episodes associated with Bipolar I Disorder (S-017).

We have completed our review of these applications, as amended, and they are approvable. Before these applications may be approved, however, you must submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling text for the package insert.

In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes.

Please submit this final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL, as soon as it is available but no more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Request for Safety Update and World Literature Update. When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update

should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

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

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of quetiapine. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include literature for all indications, but only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of quetiapine. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Request for Regulatory Update and Foreign Labeling

Please provide any new information on the regulatory status of quetiapine worldwide. We require a review of the status of all actions with regard to this drug, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we also ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. It is only necessary to provide information that is more recent than that provided in your original submission.

In addition, we ask that you provide us any current foreign labeling for quetiapine along with English translations when needed.

Request for Introductory Promotional Materials. In addition, please submit three copies of the introductory promotional materials that you propose to use for this product in these new indications. 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(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Notification of Intent to Amend the Applications. Within 10 days after the date of this letter, you are required to amend the applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Opportunity for Meeting or Teleconference. Under 21 CFR 314.102(d), you may also request a meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

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

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}
Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: FDA Draft Labeling (clean copy).

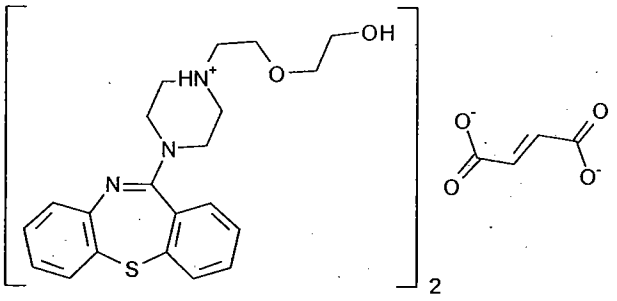
[This labeling document was created beginning with a clean version of your 12-30-02 proposal for labeling. We have made a number of changes, and these changes are explained by bracketed comments that precede the changes. Please use this document as your starting document if you wish to make further changes.]

SEROQUEL

(quetiapine fumarate) TABLETS

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 $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



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

SEROQUEL is supplied for oral administration as 25 mg (round, peach), 100 mg (round, yellow), 200 mg (round, white) and 300 mg (capsule-shaped, white) tablets.

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

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 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 acute manic episodes associated with bipolar disorder, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is 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 Mania

[We have made several changes to the following section.
-We have changed the name of this subsection to Bipolar Mania.
-We consider these 3-week studies, since the primary timepoint for analysis was specified as 3 weeks.
-We clarified that the index patients were those having manic episodes.

-We have provided an alternate description of the YMRS.
-We have made a number of other editorial changes.]

The efficacy of SEROQUEL in the treatment of acute manic episodes was established in 3 short-term 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 [ ] and 1 was adjunct therapy to [ ].

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), 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 primary outcome in these trials was change from baseline in the Y-MRS total score at Day 21.

The results of the trials follow:

Monotherapy

In two 3-week trials (n=300, n=299) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in the reduction of the YMRS total score. [ ] were dosed in a range between 400 and 800 mg per day.

Adjunct Therapy

[ ] were dosed in a range between 400 and 800 mg per day. In a similarly designed trial (n=200), SEROQUEL was associated with a similar 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 patients 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 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.

INDICATIONS AND USAGE

[ ] Mania

[We've made several changes to this section. In particular, we have characterized the trials as 3-week trials, since this was the primary timepoint for analysis.]

SEROQUEL is indicated for the short-term treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to [ ] lithium or valproate.

The efficacy of SEROQUEL in acute mania was established in two 3-week monotherapy [ ] and one 3-week adjunctive therapy trial of bipolar I patients hospitalized for [ ] (See **CLINICAL PHARMACOLOGY**). Effectiveness for more than 3 weeks has not been systematically evaluated in clinical trials. Therefore, the physician who elects to use SEROQUEL for extended periods 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

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. Two possible cases of NMS [(2/ 2792 (0.1%)] have been reported in clinical trials 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 (eg, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

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

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

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.

[The basis for adding the following language was explained in the recent correspondence you received.]

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. 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 studied. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. [redacted]

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline 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% (23/2567) of the patients treated with SEROQUEL, compared with 0% (0/ 607) 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.

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 0.6% (18/ 2792) of patients treated with SEROQUEL compared to 0.2% (1/607) 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, e.g., 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 0.4% (12/2791) 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, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients.

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 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.

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 mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% 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.

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**).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL.

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.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

[We have made several changes to the divalproex statements in this section.]

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 is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin).

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.

Geriatric Use: Of the approximately 3400 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 3000 patients. This database includes 405 patients exposed to SEROQUEL for the treatment of acute 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 3000 subjects, approximately 2700 (2300 in schizophrenia and 405 in acute mania) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 914.3 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.

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

Acute Mania: Overall, discontinuations due to adverse events were similar (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 1 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 acute 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 1. Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials[1] for the Treatment of Schizophrenia and Acute 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 2 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 2. Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials[1] for the Treatment of Acute 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%).

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: 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.

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 $\geq$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 trials the proportion of patients meeting the same weight criterion were 13% compared to 4% 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**).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo.

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) mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (2/405) for SEROQUEL compared to 0% (0/401) incidence for placebo. In acute mania (adjunct) trials the proportions of patients meeting the same criteria was 0.25% (1/405) for SEROQUEL compared to 0% (0/401) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. 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 $\geq$ 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 1 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:

[We ask that you update this section to include recently reported serious events, including, among others, rhabdomyolysis, anaphylaxis, hyponatremia/SIADH, and SJS. In addition, we ask that you update the information regarding neutropenia to include more recent experience.]

Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include [ ] [ ] 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.

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, eg, development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block.

Management of Overdosage:

[We ask that you modify the following statement to include more recent data suggesting fatal overdoses, and overdoses associated with coma, seizures, various serious cardiac events, [ ]]

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

Acute 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 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.

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 remain on it, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on SEROQUEL, 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 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.

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

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Wilmington, DE 19850
Made in USA

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/s/

Russell Katz
10/27/03 03:33:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-639/S-016 & S-017

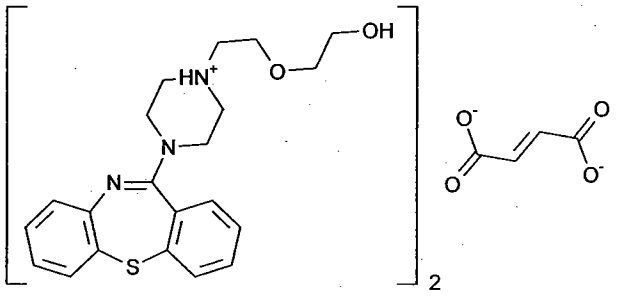
LABELING

SEROQUEL

(quetiapine fumarate) TABLETS

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), 100 mg (round, yellow), 200 mg (round, white) and 300 mg (capsule-shaped, white) tablets.

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

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 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 acute manic episodes associated with bipolar disorder, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is 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 Mania

The efficacy of SEROQUEL in the treatment of acute manic episodes was established in 3 short-term (3-week) 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 and 1 was adjunct therapy to either lithium or divalproex. 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 the Young Mania Rating Scale (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 primary outcome in these trials was change from baseline in the YMRS total score at Day 21.

The results of the trials follow:

Monotherapy

In two 3-week trials (n=300, n=299) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in the reduction of the YMRS total score. 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 patients 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 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.

INDICATIONS AND USAGE

Bipolar Mania

SEROQUEL is indicated for the short-term treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex.

The efficacy of SEROQUEL in acute bipolar mania was established in two 3-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 for more than 3 weeks has not been systematically evaluated in clinical trials. Therefore, the physician who elects to use SEROQUEL for extended periods 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
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 (eg, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

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

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

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

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% (23/2567) of the patients treated with

SEROQUEL, compared with 0% (0/607) 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.

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 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/607) 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, e.g., 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 0.4% (12/2791) 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, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients.

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.

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. 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.

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).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL.

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.

Laboratory Tests
No specific laboratory tests are recommended.

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 is indicated when SEROQUEL is administered with ketoconazole and other

inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin).

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.

Geriatric Use: Of the approximately 3400 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 3000 patients. This database includes 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 3000 subjects, approximately 2700 (2300 in schizophrenia and 405 in acute bipolar mania) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 914.3 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.

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

Acute Bipolar 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 1 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 acute 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 1. Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials[1] for the Treatment of Schizophrenia and Acute 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 2 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 2. Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials[1] for the Treatment of Acute 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%).

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: 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.

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 $\geq$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 trials the proportion of patients meeting the same weight criterion were 13% compared to 4% 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**).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo.

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. 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 $\geq$ 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 1 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: 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 events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylaxis, hyponatremia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Steven 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, eg, development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and 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

Acute Bipolar 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 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.

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 remain on it, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on SEROQUEL, 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 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.

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.

AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
Made in USA

Rev SIC 64154-

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-639/S-016 & S-017

MEDICAL REVIEW

CLINICAL REVIEW

FOOD and DRUG ADMINISTRATION

CENTER for DRUG EVALUATION and RESEARCH

DIVISION of NEUROPHARMACOLOGICAL DRUG PRODUCTS

(HFD-120)

Brand Name:	SEROQUEL ®
Generic Name:	Quetiapine [ ]
Drug Category:	Antipsychotic
Sponsor:	AstraZeneca
Indication:	Acute Mania of Bipolar Disorder
NDA Numbers:	20-639/S016;S017
Correspondence Date:	
Medical Reviewer:	Robert Levin, M.D.
Review Completed:	October 16, 2003

Table of Contents

Clinical Review for NDA 20-639

Executive Summary

I. Recommendations

A. Recommendation on Approvability

I recommend that the Division take approvable actions for quetiapine as monotherapy and as adjunctive therapy to mood stabilizers (lithium and valproate) in the acute treatment of mania (for up to 21 days) in adults with a diagnosis of Bipolar I Disorder, with or without Psychotic Features. Treatment with quetiapine can provide a clinically meaningful reduction in severity of the core features of acute mania, which include manic affect, acute agitation, hyperactivity, grandiose delusions, paranoia, hallucinations, disorganized behavior, thought disorder, dangerous and impulsive behavior, and sleep disorder. The trials demonstrate that quetiapine treatment in this population is reasonably safe and well tolerated.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Pediatric Program

I recommend that the sponsor conduct an adequate and well-controlled trial to investigate the efficacy and safety of quetiapine in treating acutely manic children and adolescents with a diagnosis of Bipolar Disorder. The sponsor has discussed plans to do so.

Long-term Efficacy and Safety Study

I recommend that the sponsor conduct studies to assess the longer-term efficacy and safety of quetiapine in the treatment of adults with Bipolar Disorder.

Of particular interest would be an examination of the potential for quetiapine to induce mania, exacerbate mania, or accelerate cycling of affective episodes in Bipolar Disorder. Reports from the literature suggest that treatment with other atypical antipsychotic drugs with similar pharmacological profiles (risperidone and olanzapine) can induce mania in patients with Bipolar Disorder. Literature suggests that one would need to monitor a large population of bipolar patients treated with quetiapine for at least 18 months, in order to adequately assess the potential risk of quetiapine in inducing mania, exacerbating mania, or accelerating affective cycling of Bipolar Disorder.

II. Summary of Clinical Findings

Executive Summary Section

A. Overview of Clinical Program

Quetiapine (Seroquel) is an atypical antipsychotic drug belonging to the class, dibenzothi-azepine derivatives. The sponsor seeks indications for quetiapine as monotherapy and as adjunctive therapy to mood stabilizers in the acute treatment of mania associated with Bipolar I Disorder, with or without Psychotic features, in adults (age≥18). The sponsor proposes stable, oral doses of 400–800 mg/day, administered BID.

The clinical mania program consisted of four trials to assess the efficacy of quetiapine. In two trials, quetiapine was used as monotherapy (IL/0104 and IL/0105), and in two trials, quetiapine was used as adjunctive therapy to the mood stabilizers, lithium or valproate (IL/0099 and IL/0100). In the 4 studies, 1,004 subjects were randomized and 992 were treated. In total, 404 subjects were exposed to quetiapine for an exposure of 49.3 patient-years. In the monotherapy trials, 208 subjects were exposed to quetiapine for a total exposure of 35.7 patient-years. In the adjunctive therapy trials, 196 subjects were exposed to quetiapine for an exposure of 13.6 patient-years. Study 0104 included 302 subjects at 50 international sites, and Study 0105 included 302 subjects at 38 international sites. Study 0099 included 191 subjects at 32 U.S. sites, and Study 0100 included 211subjects at 44 international sites.

The primary objective of each study was to assess the efficacy of quetiapine (as monotherapy or adjunctive therapy to mood stabilizers) in the acute treatment mania (for 21 days), as measured by the change in mean score on the Young Mania Rating Scale (YMRS) at Day 21. Secondary objectives included assessing the safety and tolerability of quetiapine as monotherapy and adjunctive therapy to mood stabilizers. Essentially, the trials used identical subject selection criteria, dosing regimens, efficacy endpoints, and safety variables. However, the adjunctive therapy trials recruited subjects who were treated sub-optimally with a mood stabilizer and required that subjects continue treatment with either lithium or valproate during the adjunctive therapy trials.

B. Efficacy Conclusions

Both monotherapy studies demonstrated the efficacy of quetiapine in the acute treatment of mania. In both studies, the change from baseline in mean YMRS score at Day 21 was significantly different between the quetiapine and placebo group ($p < 0.0001$ in both studies). The primary endpoint was highly appropriate for this indication. Adjunctive therapy study IL/0099 also demonstrated the efficacy of quetiapine in the acute treatment of mania. There was a statistically significant difference between the quetiapine and placebo groups in the change in mean YMRS score ($p = 0.0209$). Adjunctive therapy trial IL/0100 failed to demonstrate the efficacy of quetiapine. The difference between treatment groups in YMRS score changes was not statistically significant ($p = 0.2809$). The size of the quetiapine treatment effect, (although modest in some trials), would probably be clinically meaningful in the treatment of acutely manic patients. Compared to placebo, the effect sizes constituted a reduction on the YMRS of 4.0, 7.9, and 3.8 points for studies IL/0104, IL/0105, and IL/0099, respectively. The magnitude of the effect sizes were 1.5, 2.2, and 1.4-fold the size of the estimated placebo treatment effect for the respective studies.

In both monotherapy studies, the active control demonstrated a greater estimated treatment effect than quetiapine. In Study IL/0104, the size of the haloperidol treatment effect, compared to placebo, was a reduction of 7.4 points on the YMRS (1.9-fold the size of the placebo treatment effect). In Study IL/0105, the size of the lithium treatment effect, compared to placebo, was a YMRS score reduction of 8.5 points (2.3-fold the placebo treatment effect). The studies were not designed to make direct efficacy comparisons between quetiapine and the active controls.

It is difficult to assess the relationship of the efficacy of quetiapine to other drugs available for indication (lithium, valproate, olanzapine), since no studies have been designed to directly compare quetiapine with the other treatments. However, in Study IL/0105, the efficacy of quetiapine appeared comparable to that of lithium, when lithium was used in a manner consistent with good clinical practice. In addition, as an antipsychotic medication, quetiapine offers some benefits which the mood stabilizers, lithium and valproate do not confer. It would be useful to conduct studies specifically designed to compare the efficacy and safety of quetiapine with the approved drugs, lithium, valproate, and olanzapine.

C. Safety Conclusions

In the four trials, quetiapine treatment was reasonably safe and well tolerated as monotherapy and as adjunctive therapy to lithium or valproate. There were no new or unexpected findings with quetiapine treatment. In the four trials, 405 subjects were exposed to quetiapine and 411 were treated with placebo. The total quetiapine exposure was 49.3 patient-years. For the 21-day phases, the quetiapine exposure was 20.2 patient-years. The types and frequency of safety assessments were appropriate for this indication, and they were adequate for detecting potential safety problems. Generally, the actions taken and follow-up regarding safety problems that arose in the trials was appropriate and consistent with good clinical practice. However, the two cases of neutropenia warranted more thorough follow-up. In addition, it would have been useful to consider further monitoring of subjects who had significant decreases in thyroxine concentration.

There were 3 deaths in the trials (one in the quetiapine groups and two in the placebo groups). The death in the quetiapine group was not related to quetiapine treatment. There were fewer serious adverse events in the quetiapine groups (17) than in the placebo groups (25). Only two serious adverse events were likely related to quetiapine treatment (syncope and orthostatic hypotension). Fewer subjects in the quetiapine groups discontinued due to adverse events (24) than in the placebo groups (31). In the quetiapine groups, a significant number of adverse events leading to discontinuation were very likely related to quetiapine treatment. These adverse events were rash, seizure, asthenia, somnolence, dizziness, nausea, and various extrapyramidal symptoms (tremor, dysarthria, hypokinesia, and extrapyramidal disorder).

In the monotherapy trials, the most common adverse events associated with quetiapine treatment (versus placebo) were somnolence (16% vs. 4%), dry mouth (16% vs. 3%), extrapyramidal symptoms (13% vs. 13%), weight gain (9% vs. 2%), dizziness (7% vs. 3%), headache (6% vs. 4%), asthenia (5% vs. 2%), orthostatic hypotension (4% vs. 2%), constipation (4% vs. 1%), and fever (3% vs. 1%). As illustrated above, the proportion of quetiapine-treated subjects reporting EPS was similar to that in the placebo group. In the adjunctive therapy trials, the most commonly reported adverse events were similar to those in the monotherapy trial;

although, there were higher reporting rates of somnolence, tremor, and EPS. These findings are very likely related to concomitant treatment with either lithium or valproate. The most commonly reported adverse events in the adjunctive trials were somnolence (34% vs. 10%), extrapyramidal symptoms (21% vs. 19%), headache (17% vs. 13%), constipation (10% vs. 5%), asthenia (10% vs. 4%), dizziness (9% vs. 6%), abdominal pain (7% vs. 4%), orthostatic hypotension (7% vs. 2%), nausea (6% vs. 6%), weight gain (6% vs. 3%), and pharyngitis (6% vs. 3%). In both treatment groups, a considerable proportion of cases of EPS were due to tremor.

The safety review also focused on specific adverse events and safety findings of particular interest. As noted above, the proportion of subjects reporting EPS was very similar in the quetiapine and placebo groups for both the monotherapy and adjunctive therapy studies. There were no significant differences between treatment groups in mean glucose concentrations. The mean glucose concentration in the quetiapine groups did not change significantly. Only 6 subjects in the trials developed elevated glucose concentrations (4 in the quetiapine group and 2 in the placebo group). Quetiapine treatment was associated with weight gain in the trials (+1.8 kg in the monotherapy trials and +2.97 kg in the adjunctive trials). The mean free and total thyroxine concentrations decreased significantly (15% to 21%) in the trials, and the mean TSH concentration increased in the adjunctive therapy trials. However, relatively few subjects had abnormal thyroid function test results. Few subjects in the trials reported adverse events possibly related to abnormal serum prolactin concentration. Several subjects had elevated prolactin concentrations. However, the mean serum prolactin concentration decreased in both groups, probably due to the fact that the majority of subjects had been treated with typical antipsychotics before the trial began. Neutropenia occurred in 2 subjects in the quetiapine group and in none of the placebo group. There was one adverse event of cataract reported. There were no clinically significant findings pertaining to vital sign values, and there were no significant electrocardiogram findings.

The most commonly reported adverse events associated with quetiapine treatment are not likely to be serious, and they are manageable. These include somnolence (16%), dry mouth (16%), extrapyramidal symptoms (13%), weight gain (9%), dizziness (7%), asthenia (5%), and orthostatic hypotension (4%). As noted in labeling for quetiapine, potential serious adverse effects of quetiapine treatment include neuroleptic malignant syndrome (NMS), tardive dyskinesia (TD), orthostatic hypotension, seizures, leukopenia, neutropenia, hypothyroidism, hyperlipidemia, hyperprolactinemia, abnormal liver function, cognitive and motor impairment, priapism, dysregulation of body temperature dysregulation, dysphagia, and seizures. A number of these adverse events were reported during the trials under review, and they will be discussed in greater detail in other sections. The periodic safety update report accompanying this submission discusses a number of similar spontaneously reported serious adverse events, some of which are not currently included in labeling. These will be discussed in detail in the Periodic Safety Update Report section of this review.

Currently, it is not clear to what extent, if any, one should monitor thyroid functions, TSH, WBC and absolute neutrophil counts in patients treated with quetiapine. [ ]

[ ]

[ ]

Quetiapine has the potential to interact with drugs that are inducers or inhibitors of CYP3A4. Thus, the dose of quetiapine may need to be adjusted if coadministered with CYP3A4 inducers or inhibitors.

The relationship of the safety of quetiapine to that of other drugs indicated for the acute treatment of mania is difficult to determine, since there have been no studies designed to directly compare the safety profile of quetiapine to other available treatments.

D. Dosing

The dosing and administration regimen proposed by the sponsor is reasonable, based on the efficacy and safety results of the mania trials and based on previous experience treating schizophrenic patients. For the treatment of acute mania, the sponsor recommends initiating quetiapine treatment at 100 mg/day, divided BID, increasing by 100 mg per day to 400 mg/day on Day 4. The clinician can make further adjustments up to 800 mg/day by Day 6, in increments no greater than 200 mg/day. The sponsor states that the majority of subjects who 'responded' did so in the range of 400-[ ]mg. However, these were flexible-dose studies. Thus one cannot conclude that the trials established either a minimal effective dose or a dose-response relationship. It is possible that at least some subjects would have improved with lower doses, if the titration schedule had been more gradual.

For two reasons, I recommend that the sponsor consider altering the suggested regimen such that quetiapine would be administered as either a [ ]. Daytime somnolence was one of the most common adverse events for subjects treated with quetiapine (16% of subjects in the monotherapy studies and 26% of subjects in the adjunctive trials). Furthermore, insomnia (an important feature of acute mania) was reported by 14% of subjects treated with quetiapine in the monotherapy trial. (Only 6% of quetiapine-treated subjects reported insomnia in the adjunctive trials). [ ]

[ ]

In addition, patients might be more likely to adhere to treatment with quetiapine. Perhaps the sponsor recommends an evenly divided BID dosing due to the relatively short mean terminal half-life of quetiapine (approximately 6 hours). However, it is possible that efficacy would not be compromised by altering the suggested dosing regimen.

Age. Oral clearance of quetiapine can be reduced by 40% in elderly patients (≥65 years) compared to young patients. Dosing adjustment may be necessary in this population.

Renal Impairment. Patients with severe renal impairment (creatinine clearance = 10–30 mL/min/1.73 m^2) have a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2)[ ] Plasma quetiapine concentrations in 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 can have a 30% lower mean oral clearance of quetiapine than normal subjects. In hepatically impaired patients, AUC and Cmax can be three-fold those observed in healthy subjects. Since the liver extensively metabolizes quetiapine, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment [redacted] be necessary.

E. Special Populations

Efficacy. Quetiapine treatment was consistently efficacious, regardless of gender, race, ethnicity, geographic region, or age. The sponsor provided descriptive statistics for the estimated treatment effect within these relevant subgroups. The proportion of men and women in the studies was very similar. In the four studies, there were 479 (49%) men and 490 (51%) women. The proportion of men and women treated with quetiapine were also very similar
The monotherapy studies were conducted at numerous international sites throughout Europe, Asia, and South America, and one of the adjunctive therapy studies was conducted at numerous international sites in Europe, Canada, India, and South Africa. The other adjunctive study was conducted in the U.S. As a result, there was considerable ethnic and racial diversity among the trials. In the monotherapy trials, 63% of subjects were Caucasian, none were Black, 34% were Asian, 2% were Latino, and 1% was 'Mixed.' The various subgroups were evenly distributed among treatment groups. In the adjunctive trials, 72% of subjects were Caucasian, 10% were Black, 3% were Latino, 3% were Asian, 3% were Mixed, and 9% were 'Other.' The subgroups were evenly distributed between treatment groups. There were few subjects in the trials $\geq$ 65 years of age. Only 5% of the monotherapy population and 3% of the adjunctive therapy population were $\geq$ 65 years of age, but quetiapine appeared to be efficacious in this age group.

Safety. For subjects with hepatic insufficiency or severe renal impairment, quetiapine doses must be reduced, compared to doses used in healthy patients. Similarly, quetiapine doses may need to be reduced in elderly subjects, due to reduced clearance of quetiapine.

Pregnancy use. Quetiapine treatment has not been studied in pregnant women. It is likely that quetiapine would be used in some pregnant women with acute mania. Thus, it will be important to collect data from post-marketing reporting on women exposed to quetiapine during pregnancy. Labeling states that patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy [with quetiapine].

Pediatrics Use. Quetiapine treatment has not been studied in children or adolescents.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indications, Dose, Regimens, Age Groups

Quetiapine (Seroquel) is an atypical antipsychotic drug belonging to the class, dibenzothiazepine derivatives. The sponsor seeks indications for quetiapine, as monotherapy and as adjunctive therapy to mood stabilizers, in the acute treatment of mania associated with Bipolar Disorder, with or without Psychotic Features, in adults (age≥18). The sponsor proposes stable dosing of quetiapine in the range of 400-800 mg/day administered BID.

B. State of Armamentarium for the Indication, Acute Treatment of Mania

Three medications have been approved in the U.S. for the acute treatment of mania associated with Bipolar Disorder: 1) lithium (a mood stabilizer); 2) depakote (an anticonvulsant and mood stabilizer); and 3) olanzapine (an atypical antipsychotic medication). These medications have unique benefits, risks, and limitations in the treatment of Bipolar Disorder.

Lithium

Lithium has a role in the acute treatment of mania, acute treatment of bipolar depression, maintenance treatment of bipolar mania and depression, and prophylaxis of bipolar manic and depressive episodes. While one can use lithium effectively as monotherapy in Bipolar Disorder in some patients, clinicians frequently must use other medications in combination with lithium, in order to provide effective treatment. Commonly required concomitant medications for the treatment of acute mania include antipsychotics, benzodiazepines, and other mood stabilizers. Lithium is most useful in maintenance treatment and prophylaxis of affective episodes. The delayed onset of lithium's antimanic effect (approximately 7 to 10 days) limits its utility in the treatment of acute mania, especially as monotherapy. Moreover, lithium does not adequately treat acute psychotic symptoms or acute agitation, which are common debilitating features of an acute manic episode. Aspects of lithium's safety and tolerability profile also limit its use. For example, lithium has a relatively narrow therapeutic index regarding renal and cognitive function. Long-term use of lithium poses risks of renal dysfunction and thyroid dysfunction. In order to use lithium safely and effectively, one must regularly monitor serum lithium levels, renal function, and thyroid functions. Lithium toxicity can result in cognitive impairment, renal failure, and death. Common adverse events that can limit patients' adherence to lithium therapy include cognitive slowing, sedation, tremor, ataxia, nausea, diarrhea, and polyuria.

Valproate

Valproate can effectively treat acute mania in some patients. As with lithium therapy, valproate monotherapy often does not treat acute mania adequately; thus, the same medications used concomitantly with lithium are often required. As with lithium, the onset of antimanic effect is delayed. Furthermore, valproate does not treat psychotic symptoms and often does not treat acute agitation adequately. Valproate is not approved for maintenance therapy of mania or for prophylaxis of manic episodes associated with Bipolar Disorder. Similarly, valproate does not effectively treat or prevent depressive episodes of Bipolar Disorder. Risks associated with valproate use include hepatic dysfunction (sometimes severe, occasionally fatal); pancreatitis, weight gain, and ovarian dysfunction (polycystic ovary syndrome, irregular menses, amenorrhea). One must monitor liver function tests, hematological parameters, and valproate levels periodically.

Olanzapine

Olanzapine has been approved for the acute treatment of mania associated with Bipolar Disorder. Like risperidone, olanzapine is an atypical antipsychotic, but it belongs to a different chemical class. Olanzapine was initially

approved for acute and maintenance treatment of schizophrenia. It is used effectively in clinical practice for the treatment of psychotic symptoms, including those associated with acute manic episodes. It is not clear whether olanzapine is efficacious in maintenance treatment or as prophylaxis of manic or depressive episodes of Bipolar Disorder. Olanzapine as monotherapy has not been demonstrated to be efficacious in the treatment of bipolar depression; however, the combination of olanzapine and fluoxetine has demonstrated efficacy in treating acute depression in Bipolar Disorder. Advantages of using olanzapine in acute mania include its effectiveness in treating psychotic symptoms, acute agitation, and insomnia. Furthermore, relief of some of these symptoms can begin relatively rapidly. Potential safety and tolerability problems include extrapyramidal symptoms (akathisia, parkinsonism, dyskinesia, tardive dyskinesia), neuroleptic malignant syndrome, sedation, weight gain, hyperglycemia, and orthostatic hypotension. All of these adverse events have been associated with treatment with risperidone and other atypical and typical antipsychotic medications.

C. Important Milestones in Product Development

Quetiapine (Seroquel) was first registered in the U.K. in July 1997 for the treatment of psychosis/Schizophrenia. The drug was approved in the U.S in September 1997 for the treatment of Schizophrenia. Quetiapine was registered more widely in Europe via the mutual recognition procedure in 1999 and 2000. It is registered in more than 78 countries for the treatment of psychosis/Schizophrenia.

FDA Discussions with the Sponsor about the Quetiapine-Mania Program

Between February 15, 1999 and July 19, 2002 the Division held numerous discussions with the sponsor about plans and requirements for the clinical program and supplemental NDA submission in which the sponsor sought an indication for quetiapine in the treatment of mania associated with Bipolar Disorder. On February 15, 1999, AstraZeneca provided the Division with a clinical trial summary document for a protocol entitled "A Multicenter, Randomized, Placebo-Controlled trial of the Safety and Efficacy of SEROQUEL (quetiapine fumarate) in the Treatment of Acute Mania." The sponsor requested written input from the Division. The Division stated that two positive short-term trials in acute mania would be the minimum requirement to support a claim for short-term efficacy in this indication: one monotherapy trial and one adjunctive therapy trial that would include subjects sub-optimally treated with a mood stabilizer. A combination of these 2 short-term trials may be sufficient to support a short-term efficacy claim for monotherapy and adjunctive therapy. For assessing assay sensitivity, the Division recommended adding a third arm to the monotherapy trial in which one group would be treated with a standard mood stabilizer as monotherapy.

Other points of discussion were as follows:

1. The Division requested that the sponsor conduct an interaction study of the effects of co-administration of valproate and quetiapine.
2. The Division informed the sponsor that the 'hostility factor," would not be an acceptable secondary outcome measure.
3. The Division granted a deferral for the requirement of pediatric data in the sNDA. However, a Phase 4 program for safety and efficacy data in adolescents, including pharmacokinetic studies, would be required.
4. The Division requested that the sponsor thoroughly characterize the baseline medications and mood stabilizer treatments used by subjects prior to randomization, due to the expected heterogeneity of subjects who would be included in the adjunctive therapy trials.

II. Clinically Relevant Findings from Biopharmaceutics, Statistics, DSI Reviews

A. Statistics Review

The following is a summary of the statistics review conducted by Kooros Mahjoob, Ph.D. The statistical reviewer confirmed the efficacy findings of the sponsor. Both monotherapy trials (IL/0104 and IL/0105) demonstrated that quetiapine was efficacious in the acute treatment of mania. At Day 21, the difference in treatment effects between quetiapine and placebo was statistically significant. Adjunctive therapy Study IL/0099 demonstrated the efficacy of quetiapine as adjunctive therapy to mood stabilizers in the acute treatment of mania. At Day 21, the difference in treatment effects between quetiapine and placebo was statistically significant. Adjunctive therapy Study IL/0100 did not demonstrate the efficacy of quetiapine.

B. Biopharmaceutics Review

The following is a summary of the review conducted by the biopharmaceutics reviewer, Kofi A. Kumi, Ph.D. A comparison of the PK profile of quetiapine, when co-administered with divalproex sodium, indicated that there was no significant change in the extent of exposure (AUCs) of quetiapine. However, Cmax increased by 17%, and the 90% CI was not contained within the recommended 80 to 125% confidence limits. The increase in Max may not be clinically significant. The Cmax and AUCs of total and free valproic acid, when divalproex was administered with quetiapine, were not significantly different compared to when dival-proex was administered alone. The 90% CI for log-transformed AUC and Cmax were contained within the recommended 80 to 125% confidence limits. Dr. Kumi concluded that the results from the PK study investigating the potential for a drug interaction between divalproex sodium and quetiapine demonstrated that a clinically significant interaction would not be expected when the two drugs are co-administered. In addition, the co-administration of quetiapine with divalproex was reported to be well tolerated, and no new safety concerns were reported.

The results from a previous study submitted with the original application for Seroquel (NDA 20-639) indicated that the pharmacokinetics of lithium were not altered when co-administered with quetiapine.

C. Division of Scientific Investigation (DSI)

The reviewer from DSI, Ni A. Khin, M.D., has reported that "there are no major objectionable conditions" discovered at any of the clinical sites under review for the 4 studies. The final DSI review is pending.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Most information about the PK profile of quetiapine was generated from studies in subjects with Schizophrenia or Schizoaffective Disorder. Other than a drug interaction study of quetiapine and valproate co-administration in subjects with Bipolar Disorder, no PK studies in Bipolar Disorder subjects have been conducted.

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 Cmax and AUC values increased by 25% and 15%, respectively. The multiple-dose pharmacokinetics of quetiapine is dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable using multiple dosing. Steady-state concentrations are achieved within two days of dosing.

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. The liver extensively metabolizes Quetiapine. 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. The mean terminal half-life of is approximately 6 hours, within the proposed dose range of 400-800 mg/day.

Pharmacokinetics in Various Subgroups

Age: Oral clearance of quetiapine is reduced by 40% in elderly patients (≥65 years) compared to young patients (n=12), and dosing adjustment may be necessary

Gender: There is no apparent gender effect on the pharmacokinetics of quetiapine.

Race: There is no apparent race effect on the pharmacokinetics of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (creatinine clearance = 10–30 mL/min/1.73 m^2, have a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2; thus, dosage of quetiapine may need to be adjusted. Plasma quetiapine concentrations in 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 can have a 30% lower mean oral clearance of quetiapine than normal subjects. In hepatically impaired patients, AUC and Cmax have been three-fold those observed typically in healthy subjects. Since the liver extensively metabolizes quetiapine, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed.

Drug Interactions with Quetiapine

Co-administration of Quetiapine and Valproate
(For details, please refer to the summary of the Biopharmaceutics review in Section II.B).
1. Valproate did not produce a clinically relevant effect on quetiapine pharmacokinetics.
2. Quetiapine did not produce a clinically relevant effect on valproate pharmacokinetics.
3. Co-administration of quetiapine and valproate was generally safe and well tolerated.

Co-administration of Quetiapine and Lithium & Quetiapine and Lorazepam
The results from Study IL/0046 demonstrated that the PK profile of lithium was not altered when co-administered with quetiapine. Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics lithium, lorazepam, or antipyrine.

In Vitro Studies
In vitro enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochrome P450 isoenzymes 1A2, 2C9, 2C19, 2D6 and 3A4. Conversely, quetiapine oral clearance is increased by the CYP3A4 inducer, phenytoin, and it is decreased by the CYP3A4 inhibitor, ketoconazole. Thus, dose adjustment of quetiapine [redacted] be necessary if it is co-administered with inducers or inhibitors of CYP3A4. Quetiapine clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Smoking: Smoking has no effect on the clearance of quetiapine.

B. Pharmacodynamics
Quetiapine is a dibenzothiazepine derivative that interacts with a broad range of neurotransmitter receptors including serotonin, dopamine and adrenergic receptors. Investigators hypothesize that the combination of receptor antagonism, along with a higher selectivity for $5HT_2$ relative to dopamine D_2 receptors, contributes to its therapeutic effects.
For this submission, no pharmacodynamic studies were conducted pertaining to: 1) the mechanism of action of quetiapine; 2) selection of doses for the clinical trials; or the pharmacologic properties of quetiapine associated with adverse effects.

IV. Description of Clinical Data and Sources

A. Overall Data

The sources of data reviewed included the full efficacy and safety databases for the four clinical trials. The databases and the sponsor's summaries of efficacy and safety findings were reviewed in detail. All four studies were reviewed with equal attention to detail. One drug interaction was reviewed regarding potential interactions due to co-administration of quetiapine and valproate. In addition, the sponsor's periodic safety update report was reviewed, as were several journal articles submitted by the sponsor. Also included in this review are findings from other FDA reviewers in the biometrics, biopharmaceutics, and Division of Scientific Investigation sections.

B. Tables Listing the Clinical Trials

Table III.B.1. Quetiapine as Monotherapy in Placebo-Controlled Trials

TRIAL NUMBER DATES	TRIAL DESIGN & OBJECTIVE	STUDY DRUG REGIMENS	DISPOSITION of SUBJECTS
IL/0104 49 International sites (Europe, Asia, South America) 1-7-01 to 4-25-02	Multicenter, randomized, double-blind, placebo-controlled, parallel group, flexible-dose study to assess the anti-manic efficacy and safety of quetiapine monotherapy in subjects with Bipolar I Disorder, Manic Episode. **Duration** 21 days for primary analysis 84 days of double-blind treatment **Quetiapine Exposure** Days 1-21: 5.1 subject-years Days 1-84: 15.4 subject-years	**Quetiapine:** Flexible-dose: 100-800 mg orally, divided BID **Haloperidol:** Flexible-dose: 2-8 mg orally, divided BID **Placebo:** matching tabs; flexible-BID	Screened: 353 Randomized: 302 (86%) Treated: 299 Quetiapine: 101 Placebo: 100 Haloperidol: 98 **Discontinued [Day 21, Day 84** Discontinued: 33%, 50% Quetiapine: 35%, 46% Placebo: 40%, 58% Haloperidol: 22%, 46%
IL/0105 38 International sites (Europe & Asia) 4-3-01 to 5-27-02	(Lithium arm used for assay sensitivity instead of haloperidol. Otherwise, the study design was identical to that of IL/0104). **Duration** 21 days for primary analysis 84 days of double-blind treatment **Quetiapine Exposure** Days 1-21: 5.9 subject-years Days 1-84: 20.3 subject-years	**Quetiapine:** Flexible-dose: 100-800 mg orally, divided BID **Lithium:** Day 1: 900 mg/day. Target serum Li level: 0.6-1.4 mEq/ L **Placebo:** matching tabs; flexible-doses Orally, divided BID	Screened: 370 Randomized: 302 (82%) Treated: 302 Quetiapine: 107 Placebo: 97 Lithium: 95 **Discontinued [Day 21, Day 84** Discontinued: 18%, 42% Quetiapine: 9%, 33% Placebo: 30%, 64% Lithium: 14%, 32%

Table III.B. 2. Quetiapine as Adjunctive Therapy to Mood Stabilizers in Controlled Trials

TRIAL NO.	TRIAL DESIGN & OBJECTIVE	STUDY DRUG REGIMENS	DISPOSITION of SUBJECTS

START/ STOP DATES			
IL/0099 32 sites- U.S.	Randomized, double-blind, placebo-controlled, parallel group, multi-center, flexible-dose study to assess the anti-manic efficacy and safety of risperidone as adjunctive therapy to mood stabilizers (Lithium or Valproate) in subjects with Bipolar I Disorder, Manic Episode. **Duration**: 21 days **Quetiapine Exposure:** 3.9 subject-years	**Quetiapine + Mood Stabilizer** Flexible-dose: 100-800 mg orally, divided BID **Placebo + Mood Stabilizer:** Matching tabs; flexible-dose **Lithium** Target serum Li level: 0.6-1.4 mEq/ L **Valproate** Target serum level: 50 mg/mL to 100 mg/mL	Screened: 270 Randomized: 191 (71%) Treated: 190 Quetiapine: 90 Placebo: 100 Discontinued: 85 (45%) Quetiapine: 35 (38%) Placebo: 51 (51%)
IL/0100 44 International sites	Randomized, double-blind, placebo-controlled, parallel group, multi- center, flexible-dose study to assess the anti-manic efficacy and safety of risperidone as adjunctive therapy to mood stabilizers (Lithium orValproate) in subjects with Bipolar I Disorder, Manic or Mixed Episode. **Duration:** 21 days for the primary endpoint 42 days for the complete study **Quetiapine Exposure** Days 1-21: 5.4 subject-years Days 1-42: 9.7 subject-years	**Quetiapine + Mood Stabilizer** Flexible-dose: 100-800 mg orally, divided BID **Placebo + Mood Stabilizer:** Matching tabs; flexible-dose **Lithium** Target serum Li level: 0.6-1.4 mEq/ L **Valproate** Target serum level: 50 mg/mL to 100 mg/mL	Screened: 250 Randomized: 211 (84%) Treated : 209 Quetiapine: 106 Placebo: 103 **Discontinued [Day 21, Day 42]** Discontinued: 27%, 37% Quetiapine: 21%, 33% Placebo: 23%, 40%

C. Postmarketing Experience

Quetiapine has not been approved in other countries for the treatment of mania; however, post-marketing safety data for this indication will be discussed in the next section.

D. Review of Sponsor's Periodic Safety Update Report

D.1. Introduction and Sources of Safety Reports

The sponsor has provided a comprehensive periodic safety update that includes post-marketing data and data from clinical trials (other than those under review). The information pertains to patients treated for psychotic disorders as well as patients treated with Seroquel for mania during the post-marketing period. The safety update covers the period August 1, 2001 to July 31, 2002. The sponsor calculated patient exposure from the number of tablets delivered to wholesalers worldwide during the PSUR period. A daily dose of 300-450 mg/patient/day for schizophrenic patients has been assumed. The sponsor estimates that approximately 4 million patients worldwide have been exposed to quetiapine as of 31 July 2002. The estimated use of quetiapine was 365,000 to 547,000 patient-years, based on the average daily dose assumed above. The sponsor estimates that approximately 3,700 subjects have been exposed to Seroquel in clinical studies during the period of this PSUR.

The following types of case reports are included in the PSUR:

Spontaneous reports

All serious as well as all non-serious unlisted case reports from spontaneous notifications, which have been confirmed by a medical healthcare professional, are included. This includes all reports irrespective of causality assessment made by the reporter, i.e., even cases considered 'not related' by the reporting healthcare professional.

Spontaneous non-serious listed case reports, and medically unconfirmed spontaneous reports that originate with consumers or other non-healthcare professionals are summarized in addenda line listings and summary tabulations. These case reports are not discussed within the PSUR but have been reviewed and taken into consideration in the overall safety evaluation in Section 9.

Reports from regulatory authorities

All serious case reports received from regulatory authorities, irrespective of causality assessment, are included.

Literature reports

All serious case reports and non-serious unlisted reports from the scientific/medical literature are included if a causal relationship to the AstraZeneca drug is at least implied, as assessed by the author(s) or the company.

Reports from clinical studies

According to ICH E2C all serious case reports available from clinical studies or named patient ('compassionate') use, attributable to the drug by either the investigator or the sponsor should be included in the PSUR. This is interpreted by AstraZeneca to embrace:

- all serious cases other than those considered unlikely or not related to the drug by the investigator;
- all serious cases considered unlikely or not related to the drug by the investigator if AstraZeneca has judged that there is a suspect causal relationship to the drug;

• all serious cases not assessed by the investigator if AstraZeneca has judged that there is a suspect causal relationship to the drug;
• all serious cases where a causality assessment is unavailable from both the investigator and AstraZeneca.

Cumulative count
From case reports as defined in 6.2.1 to 6.2.4 all adverse events that are both serious and unlisted are included in the table 'Cumulative Tabulation of Serious Unlisted Reports'. Both the serious unlisted adverse events for this PSUR period and the cumulative summary tabulation from the start of the clinical program is presented.

Targeted new safety studies
Study 5077IL/0089 is a multicenter, double-blind, flexible-dose, parallel-group evaluation of the cataractogenic potential of Seroquel and Risperdal (risperidone) in the long-term treatment of patients with manifestations of psychotic disorders. This study is designed to evaluate the safety and effectiveness of Seroquel in long-term use and to further evaluate the cataractogenic potential of Seroquel. This study will be conducted to fulfill a US FDA Phase IV commitment for Seroquel and is planned for 2003.

Study 5077IL/0120 is an open-label, safety, tolerability, and steady state pharmacokinetic drug interaction study of the effect of co-administered Seroquel and Depakote Sprinkle (divalproex sodium) in patients with schizophrenic/schizoaffective disorders or in patients with Bipolar Disorder.

Published Studies
Included are 6 published articles from the pediatric literature, 5 articles regarding prolactin-related and sexual disorders literature, and one article regarding glucose regulation.

Enumeration of Safety Reports from Each Type of Source
During this period 1094 case reports met the criteria for inclusion in the safety update report. The case reports were associated with a total of 2003 adverse events. These were divided by source as follows:

Source of Report	Spontaneous	Regulatory Authority	Literature	Clinical Studies
Number of Case Reports	959	60	45	30

D.2. Sponsor'Summary of Serious Unlisted Reactions

(All safety reports in Section D pertain to Seroquel treatment of patients with diagnoses of acute and chronic psychoses including schizophrenia). Based on the information received during the reporting period of the latest PSUR, the sponsor notes that death, coma, and seizure can occur secondary to quetiapine overdose. The sponsor states that these safety issues will be brought to a Safety Evaluation Review Meeting. In addition, the sponsor notes that rhabdomyolysis, anaphylaxis, hyponatremia/SIADH, and Stevens Johnson Syndrome are serious adverse events reported for the PSUR which were previously unlisted. [ ] However, several case reports submitted by the sponsor strongly suggest that quetiapine overdose can be associated directly with several types of serious cardiac events and with NMS. These issues will be discussed in subsequent sections.

D.2.1. Overdose with Seroquel (fatalities, cardiac events, seizure, NMS)

In the current PSUR, there are three post-marketing reports of fatal overdoses with the use of Seroquel alone. There are 13 additional reports of fatal overdoses with Seroquel used in combination with one or more concomitant medications. In addition, there are two reports of seizures associated with overdose of Seroquel alone. Based on this new information, there is a need to update labeling regarding overdose with Seroquel. Currently, the overdose section states: "In clinical trials, experience with SEROQUEL in overdose is limited. Estimated doses of up to 20 g of SEROQUEL have been taken; no fatalities were reported and patients recovered without sequelae. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e. drowsiness and sedation, tachycardia and hypotension..."

A total of 50 reports involving Seroquel overdose (intentional and accidental) were reviewed for this section. Twenty-six (54.2%) of the patients who overdosed took Seroquel alone. Eighteen reports (37.5%) described patients who overdosed on multiple drugs. Four reports (8.3%) did not specify if any drugs in addition to Seroquel were taken. Two reports of overdose involved only agents other than Seroquel. Of the 48 overdose reports involving Seroquel, 19 (40%) were reported coincident with a suicide attempt or completed suicide. Included in the 19 cases is one report of a patient who used Seroquel as a means of suicide; however, the patient had not taken any Seroquel prior to the attempted suicide; and a second report of completed suicide by non-accidental overdose, in which suicide is not currently coded. These patients, including 22 females, 21 males, and 7 reports for which gender is unknown, ranged in age from 11 to 73 years. All except four reports contained information on the patient's age. The mean age for adult patients (>18 years) was 34.53 years. The ages for the five reports involving pediatric patients (<18 years) were 11, 16, 17 (2), and 18.

The estimated dose of Seroquel (when reported) taken in the 50 overdose cases reviewed (both lethal and non-lethal cases) reported ranged from 0.2 to 37 grams. Twenty-one patients recovered or were recovering at the time of this report, 16 patients had a fatal outcome, one patient had not recovered at the time of this report, and the outcome was unknown in 12 cases. Many of the AEs experienced by patients in these reports have been associated with therapeutic doses of Seroquel (somnolence, tachycardia) and others have been reported to occur with Seroquel overdose (drowsiness, sedation, tachycardia, and hypotension).

Seroquel Overdose with Fatal Outcome

There were 16 cases of overdose with a fatal outcome including 6 reports of "Overdose NOS", 1 report each of "Accidental overdose", "Drug toxicity NOS", "Therapeutic agent toxicity" and "Laboratory test abnormal NOS", and the six literature reports of implied overdose coincident with completed suicide received from "The 2000 Annual Report of the American Association of Poison Control Centers." Three patients (18.75%) overdosed with Seroquel alone, 11 patients (68.75%) used Seroquel in combination with other agents. It is uncertain in two reports if multiple agents were used (12.5%). In 10 out of 16 (62.5%) reports, the MedDRA preferred term "Completed suicide" was coded. These patients including 8 males, 3 females, and 5 patients for which gender was unspecified, ranged in age from 16 to "early 70's" (mean age = 41.06 years). The reports with a fatal outcome are described below.

The dose of Seroquel ingested was not reported in the majority (94%) of the fatal cases. However, in one report of completed suicide, the estimated Seroquel dose was 12 grams. In another case, a patient completed suicide with an overdose of 60 Seroquel tablets (strength unknown- possibly 6 grams) along with 30 tablets of Inderal (strength unknown), and an unknown NSAID (strength and quantity unknown). In one case of an elderly patient, the estimated quetiapine dose was 900 mg. In all but two reports, patients received concomitant therapeutic drugs. The majority of patients (69%) received concomitant therapy with psychotropic agents including risperidone, clozapine, lithium, fluphenazine, paroxetine, bupropion, sertraline, olanzapine, mirtazapine, venlafaxine, and unspecified tricyclic antidepressants (TCA).

Seroquel levels (various biological sources) were detected in seven (44%) reports. In one completed suicide involving Seroquel and numerous other medications, the serum Seroquel level was 2.9 mg/l. In the case of another completed suicide, the patient's serum Seroquel level was 4,700 ng/ml. This patient also had blood levels of alprazolam 59 ng/ml and mirtazapine 530 ng/ml. It is uncertain if multiple drugs including alprazolam and mirtazapine were used in the suicide attempt. In a third case, the serum Seroquel concentration was 13,960 ng/ml. In six reports, (37.5%), levels of one or more of the following drugs were detected along with Seroquel: propoxyphene, acetaminophen (APAP), aspirin, ephedrine, alprazolam, sertraline, olanzapine, mirtazapine, venlafaxine, pseudoephedrine, ethanol, and diphenhydramine.

Fatal Cases Attributed to Seroquel Overdose Alone:

2002UW02674: This report of "Overdose NOS" described an elderly (early 70's) male patient who received Seroquel (900 mg/day) for bipolar disorder. Two days after the Seroquel dose was increased from 600 to 900 mg/day, the patient was found unconscious and died. Medical history included diabetes, normopressure hydrocephalus, mild dementia, chronic obstructive airway disease (COPD), left ventricular hypertrophy, arteriosclerotic cardiovascular disease (ASCVD), microscopic infarct of the left ventricle, nephrosclerosis, and a chronic subdural hematoma. Concomitant medications included loxapine, Lamictal (lamotrigine), clonazepam, and gabapentin; however, loxapine and Lamictal were discontinued two days before the patient's death. Post-mortem blood levels of Seroquel were noted as increased at 2,990 ng/ml. Originally, the cause of death was ascribed to coronary artery disease; however, the pathologist now believes that increased Seroquel levels may have been the cause. A final autopsy report was not provided. Follow-up has been requested for full autopsy and toxicology results. [Reviewer's Note: In this complicated case involving comorbidity and polypharmacy, it may be difficult to attribute the death to Seroquel alone; although, the blood level of Seroquel was elevated].

2002SE01984: This report of "Overdose NOS" described a 27-year-old male who was treated with Seroquel for schizophrenia and previously well controlled. After two months of Seroquel therapy, the patient attempted suicide and died. The patient ingested approximately 12 grams of Seroquel in a single drug overdose. According to the physician the patient took an overdose and "got cardiac problems under the form of major troubles of the rhythm that lead to massive cardiac problems and it was no possibility for reanimation." Medical history included schizophrenia but no history of cardiac problems. Family history included "suicide caused by a jump from staircases". No further information was provided. [In this case, it appears quite possible that overdose with Seroquel alone contributed to the completed suicide].

2002AP00161: This literature report described a 36-year-old male patient who took an "accidental overdose" of Seroquel and died. The post-mortem toxicology identified only Seroquel (170 mg/L in cavity blood, 190 mg/kg in liver, and 27 mg as gastric content) and listed the manner and cause of death as accidental overdose leading to Seroquel toxicity. The patient received Seroquel for paranoid schizophrenia. No other information was provided.

Overdose and Cardiac Events

There were nine reports involving one or more of the following cardiac events associated with Seroquel overdose:"Electrocardiogram QT prolonged" (3); "Tachycardia NOS" (3); "Ventricular tachycardia" (1); "Sinus tachycardia" (1); "Arrhythmia NOS" (1); "Cardiac arrest" (1); "Cardiotoxicity" (1); and "Cardiac disorder NOS" (1). Five reports (2002AP01226, 1998UW49037, 2002PK00559, 2001AP04193, 2002SE01984) involved Seroquel alone, and four reports (2001PK00971, 2001AP02732, 2001UW15248, 2002UW06742) involved a multidrug overdose. Both patient **2002SE01984** [Arrhythmia NOS after 12 gm OD with Seroquel] and **2001UW15248** ('Cardiac Arrest' after an ingestion of probably 6 gm of Seroquel and unkown amount of propranolol) had fatal outcomes and were described above.

Overdose an QT Interval Prolongation

Three patients (2002AP01226- Seroquel OD alone), (1998UW49037- Seroquel OD alone), and (2001PK00971-Seroquel OD plus possible polypharmacy), including two females (ages 36 and 60) and one male (age 19) experienced "Electrocardiogram QT prolonged" coincident with Seroquel overdose. The Seroquel dose was 15, 6, and 9.6 grams, respectively. There was no reported history of cardiac disease for these patients. Baseline QT or QTc values were not provided. For patient 2002AP01226, post-ingestion QTc values were not provided. For patient 1998UW49037 (Seroquel OD alone) QTc intervals were recorded after the overdose: two hours post ingestion = 581 msec, 14 hours post ingestion = 710 msec, and 27 hours post ingestion = 440 msec. In the case of patient 2001PK00971, on admission, the electrocardiogram showed sinus rhythm of 88 beats per minute with prolonged QT-interval
(0.39 -0.4 s). The next day, ventricular tachycardia developed. Electrical cardioversion was considered but was not carried out due to spontaneous return to normal rhythm.

The remaining three overdose reports involving cardiac events described tachycardia (2) and increased BP (1) with Seroquel alone (2002PK00559, 2001AP04193), and cardiac disorder (unspecified) (1) with polypharmacy overdose (2001AP02732). All three patients recovered.

Overdose and Seizures

There were two reports of overdose that contained the MedDRA preferred term "Convulsions NOS" and 1 report with "Grand mal convulsion". Two reports involved an overdose of Seroquel alone (2002UW07234, 2002UW02097) and one report (2002UW06742) involved an overdose of Seroquel and gabapentin. For all three reports, information is limited and the outcome of the events is unknown. The Seroquel doses ingested were estimated to be 2,500 mg, and 5-10 grams in 2 of the cases. The quantity ingested in the third case is unkown.

Overdose in the Pediatric Population

There were five reports of Seroquel overdose in patients <18 years of age. One report (2001AP05211) described a fatal multi-drug overdose in 16-year-old patient. The dose of Seroquel was not provided. Another report (2002AP02020) described an 11-year-old female who was hospitalized after ingesting 1.3 grams of Seroquel. The patient recovered and had no evidence of cardiac toxicity, and liver function tests and serum chemistries were unremarkable. The remaining three reports (2002UW02386, 2002UW02387, and 2002UW02389) involved three teenage girls who overdosed on Seroquel and were noted to be "behaving oddly". The outcome for all three patients is unknown. All five reports are presented in more detail in the Experiences in Special Patient groups/ Pediatric Population section 9.9 of this PSUR.

Overdose and Neuroleptic Malignant Syndrome (NMS)

There were two reports of overdose in which the patients experienced "Neuroleptic malignant syndrome". The first report (2002AP00996) described a 22-year-old female who overdosed with 1500 mg of Seroquel alone. The features of the case are consistent with NMS. The second report (2001AP03934) described a 30-year-old male who received concomitant therapy with chlorpromazine. In a suicide attempt, the patient ingested 1300 mg of Seroquel, 25 mg of

chlorpromazine, and 2 mg of bromazepam. Within the day of the ingestion, the patient developed clinical and laboratory findings consistent with NMS. He recovered.

Based on the information received during this reporting period, it appears that death and seizure can occur secondary to Seroquel overdose. These issues will be brought to a SERM (safety evaluation review meeting) and any appropriate changes to the *Overdose* section 4.9 of the Seroquel CDS will be determined at that time. Prolonged QT and NMS with overdose will continue to be monitored.

Management of Overdose
It appears that the sponsor has not proposed specific labeling for the management of Seroquel overdose.

D.2.3. Rhabdomyolysis
During this reporting period, 10 serious reports containing the MedDRA preferred term "Rhabdomyolysis", were received. In addition, three reports that did not contain the preferred term "Rhabdomyolysis" but made reference to rhabdomyolysis in the narrative (2001AP04834, a serious case of blood creatine phosphokinase increased; 2001UW12114, a serious case of NMS; and 2002AP01163, a serious case of possible NMS) were received. During this reporting period, 13 reports (5 serious/8 non-serious) containing the MedDRA preferred term "Blood creatine phosphokinase increased" were received.

D.2.4. Anaphylactic/Anaphylactoid Reaction
During this reporting period, one serious report containing the MedDRA preferred term "Anaphylactoid reaction" and one serious report containing the MedDRA preferred term "Anaphylactic reaction" were received. These reports are described below. One report of anaphylactoid reaction" described a female patient who received a single dose of Seroquel (200 mg/day) and experienced a reaction similar to "anaphylactic shock reaction, symptoms included itching". Medical history included cough variant asthma and multiple allergies to inert ingredients in medications such as microcellulose, manium dioxide, many of the colorings, and magnesium stearate. No further information was provided. Microcrystalline cellulose and magnesium stearate are excipients of Seroquel. A report of "Anaphylactic reaction" described a female patient who received Seroquel for approximately one year and then experienced "laryngospasm or an anaphylactic like reaction". The patient was admitted to the intensive care unit (ICU). No further information was provided.

An all time search of the safety database for additional reports of anaphylaxis or anaphylactoid reaction revealed only one other report of anaphylaxis. This report of "Anaphylactic reaction" described a 47-year-old female patient who received Seroquel (300 mg/day) for five weeks for the treatment of schizophrenia and experienced acute delirium, which was considered to be not related to Seroquel therapy. Three weeks later, the patient was re-started on Seroquel (50 mg/day) and within hours she developed facial swelling and was hospitalized. Seroquel was discontinued and the patient recovered.

During this reporting period, four serious reports containing the MedDRA preferred term

"Hypersensitivity NOS" were received. These reports described allergic reactions involving blazing red exanthema without pruritus (2002PK00155), dizziness and swollen eyes (2002GB01215), exfoliative rash and hypotension (2002AP02297), and blueness and swelling

D.2.5. Hyponatremia/SIADH
During this reporting period, 9 reports (7 serious/ 2 non-serious) containing the MedDRA preferred term "Hyponatremia" were received. One of these reports also contained the MedDRA preferred term "Inappropriate antidiuretic hormone". Three of these reports contained a fatal outcome. The serious reports are summarized below.

D.2.6. Stevens Johnson Syndrome
During this reporting period, one serious report containing the MedDRA preferred term "Stevens Johnson Syndrome" (SJS) was received. This report described a patient who was receiving Seroquel and Depakote (valproate; labeled for SJS) and developed SJS. Depakote was discontinued. It is unknown if the SJS resolved at this point. One week later, the Seroquel dose was increased and the rash reappeared. No further information was provided.

A cumulative review of the safety database revealed only one other report. This serious report described a 9-year-old male patient with attention-deficit hyperactivity disorder, opposition defiance disorder, and a seizure disorder. While hospitalized in an acute psychiatric unit, the patient received Seroquel (50 mg 2x/day and 75 mg at bedtime), Dilantin (phenytoin; labeled for SJS), Serzone (nefazodone; labeled for SJS), and lithium. Medical history included allergic reactions to Benadryl (diphenhydramine), Depakote (valproate), and Haldol (haloperidol). After two weeks, the rash started (on 23 July 1999), worsened the following day, improved on the third day, and worsened again with fever on the fourth day. The patient took Seroquel, Dilantin, Serzone, and lithium from 16 July 1999 through 25 July 1999. (The rash was present for the last three days of drug therapy.) On the fifth day, he developed erythematous wheals and on the sixth day, he developed "possible" SJS, and was transferred to a burn unit. No other organs were affected except the skin. All medications were discontinued, and the patient is improving. On 19 July 1999, his Dilantin level was 16.8 ("within normal range"; no units provided). No further information was available.

D.3. Sponsor's Summary of Non-serious unlisted reactions
There is no evidence from the non-serious unlisted reactions reported during this PSUR period of any new safety issues.

D.4. Reviewer's Summary of Unlabelled Serious Adverse Events

Seroquel Overdose and NMS, Cardiac Events, and Pediatric Fatality
Please refer to sections above.

Hematologic Toxicity
Current Seroquel labeling lists the following adverse hematologic events: *Frequent*: leukopenia; *Infrequent*: leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia, lymphadenopathy, cyanosis; *Rare*: hemolysis, thrombocytopenia. However, the PSUR also

contains reports of serious cases that are not in current labeling. These include Pancytopenia Agranulocytosis (5), Neutropenia (22 serious/3 non-serious), Neutropenia aggravated" (2) serious), Granulocytopenia (5 serious/2 non-serious), Neutrophil count decreased (2 serious/1 non-serious), and Red Cell Aplasia (1).

The sponsor states that there were no cases of persistent severe neutropenia or agranulocytosis reported in controlled clinical trials with SEROQUEL. However, for the 2 cases of neutropenia in the mania trials under review, there was minimal follow-up of the subjects with neutropenia. The sponsor also states that during post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with SEROQUEL. Possible risk factors for leucopenia and/or neutropenia include pre-existing low white cell count and history of drug induced leucopenia and/or neutropenia. Occasionally, eosinophilia has been observed. Although signs and symptoms of bacterial infection (ie. fever, malaise, prostration and typical presentation with oropharyngeal or anorectal lesions) are commonly seen with agranulocytosis, AstraZeneca has deemed these not necessary to code for agranulocytosis. AstraZeneca defines agranulocytosis as severe neutropenia (< 0.5 x10 ^{9}/L), and the terms granulocytopenia and neutropenia as basically synonymous. Therefore, reports of neutropenia, granulocytopenia, and leukopenia will be excluded from further discussion.

Hypersensitivity NOS
During this reporting period, four serious reports containing the MedDRA preferred term "Hypersensitivity NOS" were received. These reports described allergic reactions involving blazing red exanthema without pruritus (2002PK00155), dizziness and swollen eyes (2002GB01215), exfoliative rash and hypotension (2002AP02297), and blueness and swelling of the mouth and tongue, and a dry mouth (2002AP01077). (2002GB01215 is not in the line listings of this PSUR.)

Hepatotoxicity- there were 15 reported cases of serious hepatoxic events. These included Hepatic Disorder NOS, (2), Hepatic failure (2), Hepatic function abnormal NOS (3), Hepatic pain (1), hepatomegaly (1), Hepatitis acute (1), Hyperbilirubinemia (1) Jaundice NOS (1), Hepatitis NOS (5), and Fatty liver (3).

Glucose Dysregulation- 32 cases reported (23 serious and 9 non-serious
During this reporting period, reports containing the following MedDRA preferred terms were received:
1 serious report containing "Diabetes mellitus aggravated",
1 serious report containing "Diabetes mellitus inadequate control",
1 serious report containing "Diabetes mellitus insulin-dependent",
4 (2 serious/2 non-serious) reports containing "Diabetes mellitus non-insulin-dependent",
8 (7 serious /1 non-serious) reports containing "Diabetes mellitus NOS",
3 (1 serious /2 non-serious) reports containing "Hyperglycemia",
4 non-serious reports containing "Hypoglycemia",

9 serious reports containing "Diabetic ketoacidosis", and
1 serious report containing "Diabetic coma NOS".

D.5. Spontaneous Reports in the Bipolar Disorder Population

[Seroquel Postmarketing Safety Reports with a Mania Indication (Excluding Studies 5077IL/0099, 5077IL/0100, 5077IL/0104, and 5077IL/0105) Reporting Period 01-Aug-2001 to 31-Jul-2002]

It appears that the adverse events discussed in this section may contain some overlap with the safety findings discussed in the post-marketing section for all indications, including patients with Bipolar Mania. Nevertheless, in this section, I will highlight important and unlisted findings.

Hematologic Adverse Events
Thrombocytopenia (2 cases); neutropenia (7); Agranulocytosis (2); Pancytopenia; Granulocytopenia (1); Leukopenia (7).

Cardiac Adverse Events
Death due to MI; Cardiac failure with pulmonary embolism, fever, and hyponatremia; arrhytmia, cardiac ischemia, and DKA; Atrioventricular block (2); Death related to arrhythmia NOS.

Endocrine Disorder
Hypothyroidism with weight gain and lower extremity swelling.

Ear and Eye Disorders
Tinnitus (2 cases); Bilateral Cataracts (6); Unilateral Cataract (1); Macular edema (1)

Gastrointestinal Disorders
Hypersalivation with EPS; Severe nausea and vomiting (2); Pancreatitis with elevated triglyceride levels- cotreated with valproate; Apthous ulcer (positive dechallenge and rechallenge); ulcerative colitis; glossitis and myoclonus.

Skin and Subcutaneous Tissue Disorders
Stevens Johnson Syndrome (positive dechallenge and rechallenge; Maculopapular rash (2); Rash NOS (5); Generalized edema (3); Facial edema (3); bilateral pitting edema (3);

General Disorders
Hypersensitivity reaction with jaundice, exfoliative dermatitis, and hypotension; Neuroleptic Malignant Syndrome (13); Rhabdomyolysis (2); Hepatic failure; Hepatitis; seizure after overdoes of Seroquel; Completed suicide after OD with Seroquel [serum level- 4,700 ng/ml; Death due to water intoxication and hyponatremia; Serotonin syndrome; EPS (numerous reports of the expected variety); priapism.

E. Sponsor's Literature Review

The sponsor did not submit a literature review. However, several references were provided regarding the treatment of Bipolar Disorder with various combinations of atypical antipsychotics and mood stabilizers. There are no findings in these articles that would affect the results of the sNDA review.

V. Clinical Review Methods

A. How the Review was Conducted

The four trials were reviewed separately. For each trial, the efficacy and safety data were reviewed in detail. The review was conducted by analyzing the materials listed above in section IV.A. In addition, the reviewer consulted reviews performed by members of the biometrics, biopharmaceutics, and Division of Scientific Investigations sections.

B. Overview of Materials Consulted in Review

Materials consulted included the sponsor's efficacy and safety databases, as well as the Integrated Summaries of Safety and Efficacy. These data were submitted as electronic documents. For details, please refer to Section IV.A.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The reviewer analyzed the findings of the reviewer from the Division of Scientific Investigations. In addition, our biometrics reviewer confirmed the sponsor's efficacy results. Finally, individual Case Report Forms were reviewed.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

It appears that the studies have been conducted in accordance with accepted ethical standards. The study protocols were approved by the Institutional Review Board for each study site. Names and addresses of each IRB for each center were provided by the sponsor. The sponsor states that the studies were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, which are consistent with Good Clinical Practice and applicable regulatory requirements. The sponsor has excluded subject data that was generated at sites at which study conduct was not consistent with GCP.

E. Evaluation of Financial Disclosure

The sponsor submitted the relevant documents regarding financial disclosures by investigators. Based on the findings in these documents, it does not appear that financial interests had an effect on the findings from the study. In the Financial Disclosure Summary Report- [Seroquel (5077IL)-11/14/02], the majority of investigators participating in the four studies signed documents indicating that they did not have financial arrangements which would constitute conflicts of interest. Signed documents from several investigators were not available.

VI. Integrated Review of Efficacy

A. Efficacy Conclusions

Results from monotherapy trials IL/0104 and IL/0105 demonstrate that quetiapine was efficacious in the acute treatment of mania in adults with a diagnosis of Bipolar I Disorder, Manic, with or without Psychotic Features. The statistical reviewer confirmed the efficacy findings of the sponsor. The primary endpoint, the change from baseline in mean Young-Mania Rating Scale (YMRS) score was appropriate for this indication, since it has been well validated, and it is the standard instrument used to assess the severity of mania. In Study IL/0104, the difference between the quetiapine and placebo groups in least square mean change from baseline in YMRS score was statistically significant ($p = 0.0096$). The LS mean change was –12.3 for the quetiapine group and – 8.3 for the placebo group. Thus, the size of the estimated quetiapine treatment effect is – 4.0 points on the YMRS scale (or 1.5-fold the estimated treatment effect of placebo). Although the size of the estimated quetiapine treatment effect compared to placebo appears to be modest, the effect could be clinically meaningful in the treatment of patients with acute mania. In Study IL/0105, the difference between the quetiapine and placebo groups in least square mean change from baseline in YMRS score was also statistically significant ($p < 0.0001$). The LS mean change was –14.6 for the quetiapine group and –6.7 for the placebo group. Thus, the size of the estimated quetiapine treatment effect is –7.9 points on the YMRS scale (or 2.2-fold the estimated treatment effect of placebo). The size of the estimated quetiapine treatment effect compared to placebo would be clinically meaningful in the treatment of patients with acute mania.

Results from adjunctive therapy trial IL/0099 demonstrated that quetiapine was efficacious as adjunctive therapy to mood stabilizers in the acute treatment of mania in adults with a diagnosis of Bipolar I Disorder, Manic, with or without Psychotic Features. The statistical reviewer confirmed the efficacy findings of the sponsor. The difference between the quetiapine and placebo group in mean change from baseline in YMRS score was statistically significant ($p = 0.021$). The LS mean change was –13.8 for the quetiapine group and –9.9 for the placebo group. Thus, the size of the estimated quetiapine treatment effect is –3.8 points on the YMRS scale (or 1.4-fold the estimated treatment effect of placebo). The size of the estimated quetiapine treatment effect compared to placebo is modest, but it could be clinically meaningful in the treatment of patients with acute mania. Results from trial IL/0100 did not demonstrate the efficacy of quetiapine. The difference between the quetiapine and placebo group in mean change from baseline in YMRS score (–1.97) was not statistically significant ($p = 0.281$). The LS mean change was –15.19 for the quetiapine group and –13.22 for the placebo group

B. General Approach to Review of Efficacy

The database reviewed included the full electronic efficacy database and the Integrated Summary of Efficacy submitted by the sponsor. The efficacy review was performed in consultation with the statistical reviewer, Kooros Mahjoob, Ph.D.

C. Detailed Review of the Trials

C.1. Investigators and Clinical Study Sites

Study IL/0104 was conducted at 49 clinical sites in Argentina (12 sites), Chile (3 sites), China (2 sites), Croatia (3 sites), Estonia (3 sites), Indonesia (4 sites), Latvia (3 sites), Lithuania (5 sites), Philippines (4 sites), Poland (6 sites), and Taiwan (4 sites). Study IL/0105 was conducted at 38 clinical sites in Bulgaria (6 sites), China (2 sites), Croatia (2 sites), Greece (4 sites), India (6 sites), Romania (5 sites), Russia (10 sites), and Turkey (3 sites). Study IL/0100 was conducted at 44 international sites in the following countries: U.K. (5), Belgium (4), Spain (7), Germany (6), Bulgaria (1), Romania (2), Canada (10), India (1), and South Africa (8). Study IL/0099 was conducted at 32 sites in the U.S. (A full list of clinical study sites and investigators is included in Appendix A).

C.2. Subject Selection

The inclusion and exclusion criteria listed below. They are identical for the 4 studies with the exception that, in the adjunctive therapy trials, subjects were recruited who were suboptimally treated with either lithium or valproate upon entry to the study. The adjunctive therapy trials also included subjects whom were not treated with a mood stabilizer upon entry to the study.

Key Inclusion Criteria:

1. Male or female adults (≥18 years old)
2. Diagnosis of Bipolar I Disorder, Manic (as per DSM-IV criteria)
3. Hospitalized, due to acute manic episode
4. Must have had ≥ 1 prior manic or mixed episodes which had been documented by hospitalization record or other reliable sources
5. At screening and at randomization, subjects must have had: a) a score ≥20 on the YMRS; b) a score ≥ 4 on 2 of the following YMRS items: Irritability, Speech, Content, and Disruptive/Aggressive Behavior; and c) a score ≥ 4 on the 'Overall Bipolar Illness' item of the CGI-Bipolar Severity of Illness scale.
6. Women of childbearing potential must be using a reliable method of contraception (oral hormonal contraceptive, long-term injectable or implantable hormonal contraceptive, double-barrier methods, intrauterine devices).

Key Exclusion Criteria:

1. Women who were pregnant, lactating, or cannot use a reliable method of contraception
2. Presence of a mixed episode
3. Patients with Rapid Cycling Bipolar Disorder (per DSM-IV criteria)
4. Manic index episode judged to be the direct physiological consequence of a medical condition, treatment or substance abuse
5. Hospitalization of 3 weeks or longer for the index manic episode
6. Treatment with clozapine within 28 days of the start of the trial
7. Known intolerance or lack of response to quetiapine, haloperidol (Study IL/0104), lithium (Study IL/0105) or clozapine
8. Use of the following medications:
   - Antihypertensives, if a stable dose had not been administered for at least 1 month before randomization
   - Antidepressants in the week (or a period of 5 half-lives of the drug) before randomization
   - Continuous daily use of benzodiazepines in excess of 4 mg per day of lorazepam, or the equivalent, during the month preceding screening (the week prior to randomization)
   - Potent cytochrome P450 inducers, potent cytochrome P450 3A4 inhibitors, or thioridazine in the 14 days prior to randomization
   - Depot antipsychotic medication within 1 dosing interval before randomization
9. Renal, cardiovascular, hepatic, hematological, endocrine, or clinical finding that is unstable or that in the opinion of the investigator would be negatively affected by study medication or that would affect study medication

10. Clinically significant electrocardiogram or laboratory results (including thyroid-stimulating hormone concentration more than 10% above the upper limit of the normal range, regardless of treatment for hypothyroidism or hyperthyroidism)
11. History of seizure disorder (except febrile convulsions)
12. Substance or alcohol dependence within 1 month before randomization
13. Electroconvulsive therapy (ECT) within 30 days prior to randomization

C.3. Objectives of the Study

The primary objective of each study was to evaluate the efficacy of quetiapine (as monotherapy or adjunctive therapy to mood stabilizers) in the acute treatment of mania in subjects with Bipolar Disorder, Acute Manic Episode, with or without Psychotic Features. The primary endpoint was the change in mean YMRS score at Day 21 of treatment.

The secondary objectives of the study were to evaluate the following:

1) the efficacy of quetiapine in treating depressive symptoms in subjects with acute mania
2) the efficacy of quetiapine in treating agitation and aggression in subjects with acute mania
3) the efficacy of quetiapine in treating psychotic symptoms in subjects with acute mania with psychotic features
4) the efficacy of quetiapine in improving functional status in subjects with acute mania
5) the safety and tolerability, (including the incidence of extrapyramidal symptoms), of quetiapine in subjects with acute mania

C.4. Design of the Trials

Design of the Monotherapy Trials

These were 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose studies comparing the efficacy of quetiapine, placebo and an active control in Bipolar Disorder subjects initially hospitalized for treatment of acute mania. Haloperidol was the active control in 0104, and lithium was the active control in 0105. The primary analysis pertains to the first 21 days of double-blind treatment. Patients who were screened as outpatients and subsequently required hospitalization for treatment of acute mania were eligible to participate in the study. Subjects could be discharged from the hospital beginning on Day 8, depending on their clinical condition. On Day 1, subjects were randomized to treatment with quetiapine, haloperidol or lithium, or placebo. Subjects in the quetiapine group were treated with flexible-doses of quetiapine (100-800 mg/day orally, divided BID), after an initial period of scheduled titration. Subjects in the haloperidol group were treated with flexible-doses of haloperidol (2-8 mg/day orally, divided BID) after an initial period of scheduled titration. Subjects in the lithium group were treated with lithium carbonate 900 mg/day, divided BID, beginning on Day 1. Subsequently, lithium doses were adjusted in order to achieve serum lithium levels of between 0.6 and 1.4 ng/mL.

Dosing Regimens

Quetiapine treatment was initiated at 100 mg/day on Day 1, increasing to 400 mg/day by Day 4 in increments of 100 mg/day. Allowance was made for administration of lower doses (50, 100, 150, and 200 mg/day) on Days 1-4, respectively, if a subject could not tolerate the scheduled doses. The quetiapine dose could be adjusted within the range of 200-600 mg/day on Day 5, and 200-800 mg/day on Days 6-21, based on response and tolerability.

Haloperidol treatment was initiated at 2 mg/day for Days 1 and 2. Doses were increased to 3 mg/day on Day 3, and 4 mg/day on Day 4. Allowance was made for administration of lower doses (1 mg/day on Days 1 to 3 and 2 mg/day on Day 4), depending on response and tolerability. The haloperidol dose could be adjusted within the ranges of 2-6 mg/day on Day 5 and 2-8 mg/day on Days 6 to 84, depending on response and tolerability.

Design of the Adjunctive Therapy Trials

These were 3-week, multicenter (38 in U.S.), randomized, double-blind, placebo-controlled, parallel-group, flexible-dose studies comparing the efficacy of quetiapine as adjunctive therapy to either lithium or valproate in Bipolar Disorder subjects initially hospitalized for treatment of acute mania.

Mood Stabilizer Treatment

One aim of the study was to include subjects undergoing suboptimal treatment with a mood stabilizer. Subjects were also included who were not undergoing treatment with a mood stabilizer before entry into the study. Whether or not a subject was undergoing mood stabilizer treatment before the study, the choice of mood stabilizer (lithium or valproate) for a given subject was at the discretion of the investigator, depending on the subject's medical history and previous experience with lithium and/or valproate. Subjects must have been treated with lithium or valproate stabilizer for at least 7 days within the 4 weeks immediately prior to randomization. The dosing regimen and dose titration for lithium and valproate was at the discretion of the investigator. However, the aims were to achieve symptom control, to minimize adverse effects, and to achieve target trough serum concentrations of 0.7-1.0 mEq/L for lithium and 50-100 ug/mL for valproate. Serum mood stabilizer concentrations were measured on Days 4, 7, 10, 14, and 21. Additional mood stabilizer levels were obtained as needed, at the discretion of the investigator.

C.5. Efficacy Assessments

The following efficacy assessments were used in all studies:

1. Young-Mania Rating Scale (YMRS)
2. Positive and Negative Symptom Scale (PANSS)
3. Montgomery-Asberg Depression Rating Scale (MADRS)
5. Global Assessment Scale (GAS)
6. Clinical Global Impression – Bipolar Severity of Illness & Global Improvement
7. Clinical Global Impression – Severity of Illness & Global Improvement

Efficacy assessments, (with the exception of GAS), were conducted on Days 1, 4, 7, 14, 21, 28, 42, 56, 70 and 84. GAS assessments were conducted on Days 1, 21 and 84. The key safety variables consisted of adverse events, clinical laboratory parameters, and body weight. The schedule of safety assessments will be discussed in the Integrated Analysis of Safety section.

C.6. Outcome Measures

The primary efficacy measure for all studies was the difference between the quetiapine and placebo groups in the change from baseline at Day 21 in the mean YMRS score.

The primary outcome measure is appropriate for the indication sought. However, most of the proposed secondary outcome measures would not be acceptable for inclusion in labeling. In fact, during discussions with the Division, the sponsor did not reach agreement with the Division regarding the majority of the proposed secondary outcome measures.

Proposed secondary outcome measures included the following:

1. YMRS response rate, defined as a decrease from baseline YMRS Total score of $\geq$50%
2. Time to response, defined as the interpolated time from baseline until the subject had a 50% reduction in YMRS Total score
3. YMRS remission rate, defined as a YMRS total score of $\leq$ 8 and a score of $\leq$ 2 on each of the following 4 YMRS items: Irritability, Speech, Content, and Disruptive/Aggressive Behavior
4. Change from baseline in MADRS score
5. Percentage of subjects who achieved a MADRS total score of $\geq$18 and an increase of $\geq$ 4 in MADRS score at any 2 consecutive visits after baseline, or at the subject's final visit
6. CGI-BP Global Improvement score and change from baseline in CGI-BP Severity of Illness score
7. CGI Global Improvement score and change from baseline in CGI Severity of Illness score
8. Percentage of subjects using lorazepam
9. Change from baseline in PANSS total and subscale scores
10. Change from baseline in Global Assessment Scale (GAS)
11. Change from baseline in YMRS total score at Day 84
12. Percentage of subjects who maintain their Day 21 YMRS response at Day 84
13. Percentage of subjects who maintain their Day 21 YMRS remission at Day 84

C.7. Statistical Analysis Plan

For all four studies, the sponsor used an analysis of covariance (ANCOVA) to analyze the primary and secondary efficacy variables (changes from baseline in YMRS, MADRS, and PANSS scores), using baseline scores as covariates. In order to adjust for missing data, a last observation carried forward (LOCF) approach was used in the primary assessment of each of the endpoints. Analyses were also performed using the observed case (OC) population. The Cochran-Mantel-Haenszel test was used to analyze binary variables. All statistical tests were 2-tailed with a significance level of 0.05.

C.8. Disposition of Subjects

In the monotherapy studies, 723 patients were screened, and 604 subjects were randomized and treated. In IL/0104, 55% of subjects discontinued over the course of 12 weeks (46% of the quetiapine group and 59% of the placebo group. Most of the discontinuations occurred during the first 21 days of the trial (35% of the quetiapine group and 40% of the placebo group).
In IL/0105, 42% of subjects discontinued during the 12-week trial (33% of the quetiapine group and 64% of the placebo group. During the first 21 days of the trial, 9% of the quetiapine group and 30% of the placebo group discontinued from the study.

In the adjunctive therapy trial, 520 patients were screened, and 402 subjects were randomized to treatment. In IL/0099, 38% of the quetiapine group and 51% of the placebo group discontinued from the 21-day trial. In IL/0100, 21% of the quetiapine group and 23% of the placebo group discontinued during the first 21 days of the trial. Over the course of 42 days, 33% of the quetiapine group and 40% of the placebo group discontinued from the study.

C.9. Discontinuations from the Trials

During the first 21 days of treatment in the monotherapy trials, a higher proportion of the placebo group (34%) discontinued compared to the quetiapine group (22%). Discontinuations due to lack of efficacy or disease progression accounted for 23% of the placebo group and 12% of the quetiapine group. Adverse events led to discontinuation for 4% of the placebo group and only 2% of the quetiapine group. Five percent of each treatment group withdrew consent.

During the first 21 days of the adjunctive therapy trials, the pattern of discontinuations was similar to that in the monotherapy trials. A higher proportion of the placebo group (38%) discontinued compared to the quetiapine group (28%). Discontinuations due to lack of efficacy or disease progression accounted for 16% of the placebo group and 12% of the quetiapine group. The most common reason for discontinuation was 'withdrew consent' (12% of the placebo group and 9% of the quetiapine group). Adverse events led to discontinuation for 4% of the placebo group and 3% of the quetiapine group.

C.10. Baseline Demographics & Severity of Illness

For both monotherapy studies, the baseline characteristics were very similar between the quetiapine and placebo groups. There were no meaningful differences between treatment groups in gender, age, race, weight, or body mass index. In IL/0104, there were more women than men (63% vs. 37%). A higher proportion of subjects were in the 40-64-year-old age group than in other age groups (56%). Only 6% of subjects were $\geq$ 65 years of age. Most subjects were Caucasian (74%), and 21% were Asian. The treatment groups had very similar mean severity of illness at baseline. There were similar proportions of subjects with psychotic psychotic features at baseline (42% of the quetiapine group and 44% of the placebo group). The quetiapine group had a higher proportion of severely manic subjects than the placebo group (81% versus 66%). However, the mean YMRS scores at baseline were very similar (34 in the quetiapine group and 33 in the placebo group). The mean PANSS scores were nearly identical among groups at baseline.

In both adjunctive therapy trials, the baseline characteristics were very similar between the quetiapine and placebo groups. There were no meaningful differences between treatment groups. In IL/0099, 56% of subjects were male and 44% were female. The quetiapine group had a higher proportion of male subjects (61%) than the placebo group (53%). The mean age of the treatment groups were similar (40 vs. 41), and the distribution of ages was also very similar between groups. Overall, the study population was 71% Caucasian, 19% African American, 1% Asian, 7% Latino, 1% Mixed, and 1% other. The treatment groups were similar in terms of subjects' race. The mean weight and body mass index were nearly identical between groups. The treatment groups also had very similar mean severity of illness at baseline, as determined by mean YMRS scores (32 vs.31) and by sub-categorization of mania. In each treatment group, 42% of subjects had psychotic features at baseline.

In IL/0105, there was a higher proportion of men than women (58% vs. 42%). A higher proportion of subjects were in the 18-39 age group (53%) than other age groups. Only 5% of subjects were 65 years of age or older. The proportion of Caucasian and Asian subjects were nearly equal (52% versus 48%). The treatment groups had very similar baseline severity of

illness. The mean baseline YMRS scores were 33 for the quetiapine group and 34 for the placebo group. The mean PANSS scores at baseline were nearly identical (58 versus 59). The placebo group had a higher proportion of subjects with psychosis (34%) than the quetiapine group (26%). The difference was probably not meaningful, given the other baseline severity scores.

In study IL/0100, fifty percent (50%) of subjects were men, and 50% were women. The distribution was nearly identical within each treatment group. The mean age of subjects in the study was 39.5 years, which was nearly the same in each treatment group. In the study, 73.5% of subjects were Caucasian, 1.5% were African American, 0.5% were Latino, 4.5% were Asian, 4% were Mixed, and 16% were classified as "Other." The racial distribution was very similar between the treatment groups. The mean weight and body mass index were nearly identical between treatment groups. The baseline severity of illness was very similar between groups, based on YMRS scores (32 vs. 33). However, the quetiapine group had a higher proportion of subjects with psychotic features (49%) compared to the placebo group (42%).

C.11. Pre-Trial Antipsychotic and Mood Stabilizer Exposure

Monotherapy Trials

In both IL/0104 and IL/0105, the extent and type of pre-trial exposure to antipsychotic and mood stabilizer medications was similar between the quetiapine and placebo groups. In the 28 days prior to the Study IL/0104, most subjects had been treated with a typical antipsychotic (74% of the quetiapine group and 71% of the placebo group). A small proportion had been treated with olanzapine (5% and 5%), and a small proportion had been treated with risperidone (7% and 5%). None of the subjects in any group had been treated with quetiapine before the trial. A significant proportion of subjects in each group had not been treated with an antipsychotic medication in the 28 days prior to the study (22% and 23%). The mean duration of typical antipsychotic use in the pre-trial period was approximately 11 days in each group, and the median duration was 9 days in each group. The mean and median duration of atypical antipsychotic use was also similar in the treatment groups.

As in IL/0104, in the 28 days prior to Study IL/0105, most subjects had been treated with a typical antipsychotic (68% in both the quetiapine and placebo groups). A small proportion had been treated with olanzapine (1% vs. 1%), and a small proportion was treated with risperidone (5% vs. 4%). A small proportion of subjects had been treated with quetiapine before the trial (7% vs. 2%). A significant proportion of subjects in each group were not treated with an antipsychotic medication in the 28 days prior to the study (27% and 30%). The mean duration of typical antipsychotic use before the trial was similar among the groups (12, 10 days). The median duration was 8 days in each group. The mean and median duration of risperidone and quetiapine treatment was very similar between groups.

In both monotherapy trials, most subjects had not been treated with a mood stabilizer in the 28 days prior to the study (72-81%). The types and duration of mood stabilizer use before the trials were similar between treatment groups. In IL/0104, 77% of the quetiapine group and 72% of the placebo group had been treated with a mood stabilizer. A significant proportion of subjects had

been treated with lithium (17% in each group). A small proportion of subjects had been treated with valproate (4% and 8%), and a small proportion of subjects had been treated with 'other' mood stabilizers (5% and 7%). The duration of mood stabilizer use was similar between treatment groups. The mean duration of lithium use was 14 and 10 days, respectively, and the median duration was 14 and 8 days, respectively. The mean duration of valproate use was 10 and 11 days, respectively, and the median duration was approximately 10 days in each group. The mean duration of 'other' mood stabilizers was 12 and 11 days, respectively, and the median duration was 9, 9, and 11 days, respectively.

In IL/0105, 77% of the quetiapine group and 81% of the placebo group had been treated with a mood stabilizer. In the quetiapine group, 17% of subjects had been treated with lithium. In the placebo group, 12% of subjects had been treated with lithium. A small proportion of subjects had been treated with valproate (5% vs. 4%), and a small proportion of subjects had treated with 'other' mood stabilizers (6% vs. 8%). The duration of mood stabilizer use was similar between treatment groups. The mean duration of lithium use was 16 and 16 days, respectively, and the median duration was 17 and 14 days, respectively. The mean duration of valproate use was 13 and 15 days, respectively, and the median duration was approximately 12 days in each group. The mean duration of 'other' mood stabilizers was 9 and 6 days, respectively. The median duration was 9 and 4 days, respectively.

Adjunctive Trials

In the 28 days prior to the adjunctive therapy trials, most subjects were treated with an antipsychotic medication. For both trials, the types of antipsychotic use were similar between the quetiapine and placebo groups. In U.S. Study IL/0099, 68% of the quetiapine group and 58% of the placebo group had been treated with antipsychotic medications prior to the trial. The most commonly used medication were olanzapine (33% and 30%), and risperidone (25% and 18%). Twenty-one percent (21%) of the quetiapine group and 25% of the placebo group used typical antipsychotics. A small proportion of subjects had been treated with quetiapine before the trial (10% and 9%). Although the proportion of subjects using antipsychotics before the trial was higher in the quetiapine group, it is not clear whether the difference could be potentially significant, since data regarding the duration of antipsychotic use before the trial was not available.

In Study IL/0100, 74% of the quetiapine group and 78% of the placebo group had been treated with antipsychotic medication before the trial. Most subjects were treated with typical antipsychotic medications (61% of the quetiapine group and 62% of the placebo group). Sixteen percent (16%) of the quetiapine group and 17% of the placebo group had been treated with olanzapine. Risperidone had been used by 11% and 10% of the quetiapine and placebo groups, respectively. A small proportion of subjects had been treated with quetiapine before the trial (5% of each group). Data were not available regarding the duration of antipsychotic medication use for the 28-day period before the trial.

In the 28 days prior to trial IL/0099, most subjects (95%) had been treated with a mood stabilizer (96% and 95% of the quetiapine and placebo group, respectively). The pattern of mood stabilizer use prior to the study was similar between the quetiapine and placebo groups. More

subjects had been treated with valproate than with lithium (60% and 58% of the quetiapine and placebo group, respectively). Moreover, the pattern of continuous use of assigned mood stabilizer prior to randomization was similar between treatment groups. The majority of subjects (52%) had been treated with either lithium or valproate for $\geq$ 22 days before beginning study treatment (51% and 53% of the quetiapine and placebo groups, respectively). Only 4% of subjects were treated continuously with a mood stabilizer for 15-21 days. For the interval 8-14 days, a substantial proportion of subjects had been treated with mood stabilizers (26% and 28% of the quetiapine and placebo group, respectively). For the interval 1-7 days, 14% and 12% of the quetiapine and placebo groups, respectively, had been treated continuously with a mood stabilizer. In summary, there was no significant difference in the type or duration of mood stabilizer use between treatment groups.

In IL/0100, the pattern of continuous use of assigned mood stabilizer prior to randomization was similar between the quetiapine and placebo group. In the 28 days prior to the trial, most subjects had been treated with a mood stabilizer (96% and 95% of the quetiapine and placebo group, respectively). Overall, more subjects were treated with lithium than valproate (83% in each treatment group). Approximately 25% of subjects had been treated with either lithium or valproate for $\geq$ 22 days prior to beginning study treatment (24% and 25% of the quetiapine and placebo groups, respectively). Only 16% of subjects in each group were treated continuously with a mood stabilizer for 15-21 days. For the interval 8-14 days, a substantial proportion of subjects had been treated with mood stabilizers (44% and 47% of the quetiapine and placebo group, respectively). For the interval 1-7 days, 9% and 5% of the quetiapine and placebo groups, respectively, had been treated continuously with a mood stabilizer. In summary, there was no significant difference in the type or duration of mood stabilizer use between treatment groups.

C.12. Treatment Dose

In Study IL/0104 at Day 21, the mean of the last week median dose of quetiapine was 559 mg/day. At Day 84, the mean of the last week median dose of quetiapine was 532 mg/day. The mean cumulative dose per subject was 30,329 mg. In Study IL/0105 at Day 21, the mean of the last week median dose of quetiapine was 586 mg/day mg. At Day 84, the mean of the last week median dose of quetiapine was 651 mg/day mg. The mean cumulative dose of quetiapine per subject was 43,473 mg in Study IL/0105.

In Study 0099 at Day 21, the mean of the last week median dose of quetiapine was 584 mg/day. The mean cumulative quetiapine dose per subject was 7,952 mg. In Study 0100 at Day 21, the mean of the last week median dose of quetiapine was 423 mg/day. The median daily dose of quetiapine during the last week of treatment (Day 42) was 455 mg. The mean cumulative quetiapine dose per subject was 15,229 mg.

C.13. Mood Stabilizer Assignment for the Adjunctive Therapy Trials

In Study 0099, more subjects were treated with valproate (59%) than with lithium (41%). In the quetiapine group, 60% of subjects were treated with valproate, and 40% were treated with lithium. In the placebo group, 58% of subjects were treated with valproate, and 42% were treated with lithium. Thus, the assignments of mood stabilizers were similar in the treatment groups at baseline. In Study 0100, a higher proportion of subjects were treated with lithium

(83%) than with valproate (17%). This was largely due to the fact that, in many countries, valproate had not been approved as a treatment for mania. In the quetiapine group, 83% of subjects were treated with lithium, and 17% were treated with valproate. In the placebo group, 83% of subjects were treated with lithium and 17% were treated with valproate. Thus, the assignments of mood stabilizers were very well balanced between treatment groups at baseline.

C.14. Mean Serum Concentrations of Mood Stabilizer Medications

In both adjunctive therapy studies, the mean serum concentrations of lithium and valproate were relatively low, compared to the concentrations targeted in the protocol and compared to mood stabilizer levels typically targeting in the clinical treatment of acute mania. In Study 0099, the mean lithium levels ranged from 0.74-0.8 meq/L, and mean valproate levels ranged from 68.3-74.6 ug/mL. The mean concentrations of lithium and valproate were quite similar between the quetiapine and placebo groups.

As in Study IL/0099, the mean lithium and valproate concentrations in Study IL/0100 were near the lower range of the serum concentrations targeted. Mean lithium levels ranged from 0.74-0.8 meq/L, and mean valproate levels ranged from 68.3-74.6 ug/mL. The mean concentrations of lithium and valproate were quite similar between the quetiapine and placebo groups. The mean lithium level was 0.74 meq/L for both treatment groups. The mean valproate levels were 66 in the quetiapine group and 68.3 ug/mL in the placebo group.

The sponsor notes that, for the pooled adjunctive therapy trials, approximately 25% of subjects in the quetiapine group and 20% of subjects in the placebo group did not have median mood stabilizer levels within the targeted range (0.7 to 1.0 mEq/L for lithium and 50 to 100 ug/ml for valproate). The sponsor states that any potential source of bias that this may have intro-duced was examined by the exclusion of these subjects from the per protocol analyses, the results of which were consistent with the MITT analysis.

C.15. Concomitant Medications Permitted and Prohibited

Permitted Psychotropic Medications

Concomitant psychotropic medications permitted during the studies included:

1. Zolpidem, chloral hydrate, zopiclone, and zaleplon were permitted for alleviation of insomnia, provided that the specified maximum doses were not exceeded and that only 1 sleep medication was used on any single study day
2. Lorazepam or other benzodiazepines for agitation (but not insomnia) was permitted as specified: up to 6 mg/day from screening to Day 4; up to 4 mg/day from Day 5 to Day 7; up to 2 mg/day from Day 8 to Day 10, and up to 1 mg/day from Day 11 to Day 14. Lorazepam use was not permitted after Day 14 and was to be withheld for 6 hours before psychiatric assessments were conducted. (Doses of benzodiazepine were to be converted to the equivalent doses of lorazepam and administered according to the criteria outlined above).

Prohibited Medications

Use of any psychoactive drugs including antidepressant, mood stabilizer, or antipsychotic, was not permitted during the 84-day trial, beginning at randomization (other than lorazepam and sedative/hypnotic drugs as specified above). Use of cytochrome P450 inducers, potent inhibitors, and thioridazine, was prohibited.

Lorazepam Used During the Study- Monotherapy and Adjunctive Trials
In summary, it is unlikely that lorazepam use conferred a treatment effect in any of the trials; however, data regarding the doses of lorazepam used were not provided by the sponsor. Such data would be necessary for fully analyzing a potential treatment effect of lorazepam between treatment groups. The data were presented as the proportion of subjects from the MITT population who were treated with lorazepam each day. Thus, the proportion using lorazepam on any given day will not reflect the number of subjects who have discontinued from each group. As a result, the lorazepam may not be entirely meaningful. From the data presented, it appears that the proportion of subjects using lorazepam during the first 14 days of the study was generally similar in the treatment groups for all trials and decreased over time in each group. The proportion of subjects using lorazepam in the quetiapine groups ranged from 41-66%, and the proportion using lorazepam in the placebo groups ranged from 57%-80%.

Sedative Use During the Trials
It is unlikely that use of sedative medications would have affected the efficacy results, based on the proportions of subjects in each treatment group using such medications. However, the sponsor did not provide data regarding the doses of sedatives used. At each time point in all four trials, the quetiapine groups had a lower proportion of subjects using medications for sleep than did other groups. The proportion of the quetiapine group using these medications steadily declined during the first 21 days at a faster rate than the decline in the placebo groups.
The proportion of the quetiapine group using sedatives ranged from 48% to 56%, and the proportion of the placebo groups using sedatives ranged from 59% to 66%.
Overall, 55% of the quetiapine group and 63% of the placebo group used at least one dose of sedative medication. Over time, the numbers of subjects using sedatives steadily decreased. It is unlikely that the use of sedative medications could have affected the results of the study.

Anticholinergic Medication Use During the Trials
In all four trials, a relatively small proportion of subjects treated with quetiapine used anticholinergic medications to treat EPS. This observation is consistent with the relatively low proportion of subjects reporting EPS as adverse events. The proportion of subjects in the quetiapine groups using anticholinergic medications ranged from 6% to 11%, and the proportion of subjects in the placebo groups using anticholinergic medications ranged from 8% to 13%. Thus, the extent of anticholinergic use was comparable between the quetiapine and placebo groups.

D. Efficacy Results and Conclusions

D.1. Sponsor's Analysis of the Monotherapy Trials

The sponsor's efficacy results from the monotherapy trials are summarized in the table below.

Table 1. Sponsor's Results Using LOCF Method- Change in mean YMRS Scores

Day of		Study IL/0104		Study IL/0105	
		Treatment	Comparison	Treatment	Comparison

Assessment	Attribute	Qtp	Pla	Hal	Qtp - Pla	Hal - Pla	Qtp - Hal	Qtp	Pla	Lit	Qtp - Pla	Lit - Pla	Qtp – Lit
Day 21	N (MITT)	101	100	98	--	--	--	107	95	98	--	--	--
	Mean Δ	-12.29	-8.32	-15.71	-3.97	-7.39	3.42	-14.62	-6.71	-15.20	-7.92	-8.49	0.57
	P-Val	--	--	--	0.0096	<0.0001	SIG	--	--	--	<0.0001	<0.0001	N-SIG
Day 84	N (MITT)	101	100	98	--	--	--	107	95	98	--	--	--
	Mean Δ	-17.52	-9.48	-18.92	-11.83	-13.26	1.40	-20.28	-9.00	-20.76	-11.28	-11.75	0.48
	P-Val	--	--	--	<0.0001	<0.0001	N-SIG	--	--	--	<0.0001	<0.0001	N-SIG

Sponsor's Primary Efficacy Results- Study IL/0104

At baseline, the mean YMRS scores were similar between the quetiapine and placebo groups (33.9 and 33, respectively). For the primary endpoint, the change in mean YMRS score at Day 21, the quetiapine group had a greater decrease (−12.3) than the placebo group (−8.3). The difference (−4.0) was statistically significant (p= 0.0096). In the haloperidol group, the change in mean YMRS score (−15.7) was also statistically significant, compared to placebo group ($p < 0.0001$). Although the reduction of YMRS score was greater in the haloperidol group than in the quetiapine group, the difference between these groups was not statistically significant. The size of the estimated treatment effect of quetiapine, compared to placebo,
Was −4.0 points on the YMRS, or approximately 1.5-fold the estimated placebo treatment effect. The quetiapine effect appears to be modest; however, it could be clinically significant in the acute treatment of mania. The size of the estimated treatment effect of haloperidol compared to placebo is −7.4 points on the YMRS, or approximately 1.9-fold the estimated treatment effect of placebo. The haloperidol effect would be clinically significant in the acute treatment of mania.

The results also demonstrate that both quetiapine and haloperidol were efficacious in the treatment of mania at the end of 84 days of double-blind, placebo-controlled treatment. At Day 84 the change from baseline in mean YMRS score for the quetiapine group was −17.5, compared to −9.5 for the placebo group. The difference was statistically significant
($p < 0.0001$). Similarly, the difference between the haloperidol and placebo groups was statistically significant ($p< 0.0001$). The difference between the quetiapine and haloperidol groups was not statistically significant. The sizes of the estimated treatment effects for both quetiapine and haloperidol would be clinically significant in the treatment of acutely manic patients. Note that the magnitude of reduction in YMRS scores at Day 84 was not dramatically different than the reductions observed at Day 21.

Sponsor's Efficacy Results- Study IL/0105

At baseline, the mean YMRS scores were similar in the quetiapine, placebo, and lithium groups (32.7, 34, and 33). For the primary endpoint, the change in mean YMRS at Day 21, the quetiapine group had a greater decrease (−14.6) than the placebo group (−6.7). The LS mean difference (−7.9) was statistically significant ($p < 0.0001$). In the lithium group, the change in mean YMRS score (−15.2) was also statistically significant, compared to placebo group ($p < 0.0001$). The difference between the quetiapine and lithium groups was not statistically significant. The size of the estimated quetiapine treatment effect, compared to placebo, was –7.9 points on the YMRS, or approximately 2.2-fold the estimated treatment effect of placebo. The

size of the estimated lithium treatment effect, compared to placebo, was – 8.5 points on the YMRS, or 2.3-fold the estimated placebo treatment effect. The size of the treatment effect for quetiapine would be clinically significant in the treatment of acutely manic patients.

At Day 84, the results demonstrated that quetiapine was efficacious in the treatment of mania. The differences in changes in mean YMRS score between the quetiapine and placebo groups was statistically significant, in favor of quetiapine ($p < 0.0001$). Similarly, the difference between the lithium and placebo group was statistically significant ($p < 0.0001$). The difference between the quetiapine and placebo groups was not statistically significant.

D.2. Statistical Reviewer's Analysis of the Monotherapy Trials

The statistical reviewer's efficacy results are summarized in the table below. The results of the analysis confirm the sponsor's results.

Table 2. Reviewer's Results of Monotherapy Trials using MMRM- Change in YMRS Scores

Day of Assessment	Attribute	Study IL/0104						Study IL/0105					
		Treatment			Comparison			Treatment			Comparison		
		Qtp	Pla	Hal	Qtp - Pla	Hal - Pla	Qtp - Hal	Qtp	Pla	Lit	Qtp - Pla	Lit - Pla	Qtp – Lit
Day 21	N (MITT)	101	100	98	--	--	--	107	95	98	--	--	--
	Mean Δ	-13.14	-8.80	-16.37	-4.34	-7.19	2.86	-16.07	-8.61	-17.29	-7.56	-9.00	1.44
	P-Val	--	--	--	0.0089	<0.0001	0.0783	--	--	--	<0.0001	<0.0001	0.3979
Day 84	N (MITT)	101	100	98	--	--	--	107	95	98	--	--	--
	Mean Δ	-18.86	-10.62	-20.18	-8.92	-7.61	-1.32	-17.37	-12.90	-18.78	-4.31	-5.91	1.59
	P-Val	--	--	--	<0.0001	<0.0001	0.4478	--	--	--	0.0001	0.0001	0.2344

Statistical Reviewer's Primary Efficacy Results- Study IL/0104

The statistical reviewer performed a Mixed-Effects Model, Repeated Measure (MMRM) analysis. The methodology utilizes all available information for each subject, from baseline to the point of discontinuation or completion of study. In summary, the reviewer confirmed the sponsor's efficacy results for the analyses at Day 21 and Day 84. There were some minor, inconsequential numerical differences, compared with the sponsor's results. At Day 21, the difference between the quetiapine and placebo groups in mean change in YMRS scores (−4.3) was statistically significant (p= 0.0089). The difference in YMRS score changes between the haloperidol and placebo groups (−7.2) was also statistically significant (p< 0.0001). However, the difference between the quetiapine and haloperidol group (−2.85), favoring haloperidol, was not statistically significant (p= 0.078). Using the MMRM analysis, the size of the estimated quetiapine treatment effect compared to placebo is −4.3 points on the YMRS, or 1.5-fold the estimated treatment effect of placebo, which is comparable to the size of the estimated treatment effect using the ANCOVA analysis with LOCF. The size of the estimated haloperidol treatment effect is −7.2 points on the YMRS, or 1.9-fold the estimated placebo effect. While the estimated quetiapine effect size seems modest, it could be clinically meaningful in the treatment of acutely manic patients.

Statistical Reviewer's Efficacy Results- StudyIL/0105

At Day 21, the difference in mean YMRS scores changes between the quetiapine and placebo groups (−7.56) was statistically significant (p< 0.0001). The difference between the lithium and placebo groups (−9.0) was also statistically significant (p< 0.0001). However, the difference between the quetiapine and placebo groups was not statistically significant. For the 21-day phase, the size of the estimated quetiapine treatment effect was – 7.56 YMRS points, or 1.9-fold the estimated treatment effect size of placebo, which is similar to the treatment effect determined using the sponsor's method. At Day 84, the treatment difference between the quetiapine and placebo groups was statistically significant (p = 0.0001). The difference between the lithium and placebo groups was also statistically significant (p = 0.0001). The difference between the quetiapine and lithium groups was not statistically significant

D.3. Adjunctive Therapy Trials- Sponsor's Efficacy Results

Table 3. Sponsor's Results of Adjunct Therapy Trials- Change in Mean YMRS Scores

Day of Assessment	Attribute	Study IL/0099			Study IL/0100		
		Treatment		Comparison	Treatment		Comparison
		QTP + LI/DVP	PLA + LI/DVP	QTP - PLA	QTP + LI/DVP	PLA + LI/DVP	QTP - PLA
Day 21	N (MITT)	81	89	--	104	96	--
	Mean Δ	-13.76	-9.93	-3.82	-15.19	-13.22	-1.97
	P-Val	--	--	0.0209	--	--	0.2809
Day 42	N (MITT)	--	--	--	104	96	--
	Mean Δ	--	--	--	-17.10	-14.27	-2.83
	P-Val	--	--	--	--	--	N-SIG

Sponsor's Efficacy Results- Study IL/0099

The results demonstrate that quetiapine, as adjunctive therapy to mood stabilizers, was efficacious in the acute treatment of mania. The difference in the changes in YMRS score between the quetiapine and placebo group (–3.8) was statistically significant (p = 0.0209). The size of the estimated treatment effect was – 3.8 points on the YMRS, or 1.4-fold the estimated treatment effect of placebo. Such a quetiapine treatment effect size is modest, but it could be clinically meaningful in the treatment of patients with acute mania. At Day 42, the difference in YMRS score changes between the quetiapine and placebo group was not statistically significant.

Sponsor's Efficacy Results- Study IL/0100

At Day 21, the LS mean difference between treatment groups was –1.97, which was not statistically significant (p = 0.2809). At Day 84, the difference between groups (-2.83) was also not statistically significant.

D.4. Statistical Reviewer's Efficacy Analysis- Adjunctive Therapy Trials

Table 4. Reviewers Results of Adjunct Therapy Trials- Change in Mean YMRS Scores

Day of Assessment	Attribute	Study IL/0099			Study IL/0100		
		Treatment (Raw Means)		Comparison LS Means	Treatment		Comparison
		QTP + LI/DVP	PLA + LI/DVP	QTP - PLA	QTP + LI/DVP	PLA + LI/DVP	QTP - PLA
Day 21	N (MITT)	81	89	--	104	96	--
	Mean Δ	-12.42	-9.03	-5.64	-12.35	-11.30	-0.8783
	P-Val	--	--	0.0025	--	--	0.6244
Day 42	N (MITT)	--	--	--	104	96	--
	Mean Δ	--	--	--	-17.10	-14.27	-1.30
	P-Val	--	--	--	--	--	0.5079

Statistical Reviewer's Efficacy Results- Study IL/0099

Results of the MMRM analysis confirm that quetiapine, as adjunctive therapy to mood stabilizers, was efficacious in the acute treatment of mania. The difference in the change in mean YMRS scores between the quetiapine and placebo groups (–5.6) was statistically significant (p = 0.0025). The size of the estimated quetiapine treatment effect was – 5.6 points

on the YMRS, or 1.4-fold the estimated treatment effect of placebo, which is quite similar to the estimated effect size determined when using the sponsor's analysis.

Statistical Reviewer's Efficacy Results- Study IL/0100

Using a MMRM analysis, the statistical reviewer confirmed that the trial did not demonstrate the efficacy of quetiapine at Day 21 or Day 84. With this model, the between-treatment difference (–0.88) was not statistically significant (p = 0.6244) at Day 21.

D.5. Sponsor's Analysis of Secondary Efficacy Measures

In IL/0104, the mean CGI-Severity scores, the differences between treatment groups in LS mean change was statistically significant (p= 0.0399), favoring quetiapine treatment. This result might be considered supportive of the conclusion that quetiapine was efficacious in this trial. As noted above, the sponsor did not reach agreement with the Division regarding most of the proposed secondary efficacy measures. Most would not be acceptable for various reasons, primarily because the measures were redundant or pseudospecific. Although not supportive of the trial results, the following proposed secondary efficacy measures were positive: PANSS (p= 0.006); MADRS (p= 0.005); and GAS (p= 0.023). Results of other secondary outcome measure analyses were not positive. Secondary endpoints that failed included: the difference in response rates; the difference in remission rates; CGI-Improvement scores; and CGI-Bipolar measures.

In IL/0105, several of the sponsor's proposed secondary efficacy measures were positive at Day 21. These include: CGI-Bipolar-Severity of Illness ($p < 0.0001$); CGI-BP-Improvement ($p < 0.0001$); CGI-Severity ($p < 0.0001$); CGI-Improvement ($p < 0.0001$); and PANSS Total ($p = 0.006$). The global measures might be considered supportive of the primary efficacy results; however, the points discussed in the analysis of Study 0104 apply to this study as well.

In IL/0099, the CGI-Bipolar Severity and the CGI-Bipolar Global Improvement results were both positive ($p = 0.0013$, and $p = 0.012$, respectively). The analysis for the PANSS Total score did not demonstrate statistical significance ($p = 0.323$). The results of the global ratings might be considered supportive of the primary efficacy results.

D.6. Subgroup Analysis

In both monotherapy trials, subgroup analysis demonstrated that quetiapine was consistently efficacious, regardless of the presence or absence of psychotic features, gender, race or ethnicity, or age. In the subgroup with psychotic symptoms (N = 86), quetiapine treatment had a numerical advantage over placebo treatment. The estimated mean difference from placebo was –5.8 points on the YMRS for the quetiapine group. In the subgroup without psychotic symptoms at baseline (N = 115), there was a larger estimated mean difference, compared to placebo (–10.1). Thus, efficacy of quetiapine was consistent, regardless of the presence or absence of psychotic features at baseline. Similarly, for both men (N = 74) and women (N = 127), quetiapine treatment had a numerical advantage over placebo. The estimated treatment effect was somewhat larger for women than men. The mean differences from placebo were –9.5 for women and –7.0 for men. In addition, the efficacy of quetiapine was consistent across racial subgroups. The study population was 77% Caucasian, 2% Latino, 19% Asian, and 3% Mixed. In the respective subgroups, the mean differences in the quetiapine group compared to the placebo group were –

8.2, –24.5, –8.4, and –6.2. Finally, for the age subgroups, 18-39 (N = 82), 40-64 (N = 112), and ≥ 65 (N = 7), the estimated differences between the quetiapine and placebo groups were – 6.4, - 9.3, and – 20.5, respectively. The efficacy of quetiapine was consistent across age groups.

In IL/0105, subgroup analysis based on the presence or absence of psychotic symptoms demonstrated that, in the subgroup with psychotic symptoms (N = 60), quetiapine treatment had a numerical advantage over placebo treatment. The estimated mean difference from placebo was –11.1 points on the YMRS for the quetiapine group. In the subgroup without psychotic symptoms at baseline (N = 142), the estimated mean difference was –10.4. Thus, efficacy of quetiapine appears to have been consistent, regardless of the presence or absence of psychotic features at baseline. For both men (N = 115) and women (N = 87), quetiapine treatment had a numerical advantage over placebo. The estimated treatment effect was somewhat larger for women than men. The mean differences from placebo were –15.4 for women and –7.5 for men. The study population was 52% Caucasian and 48% Asian. In the respective subgroups, the mean differences in the quetiapine group compared to the placebo group were – 17.1 and – 5.9. Thus, it appears that quetiapine was consistently efficacious across the two racial groups. For the age subgroups, 18-39 (N = 102), 40-64 (N = 92), and ≥ 65 (N = 8), the estimated differences between the quetiapine and placebo groups were – 9.0, - 13.4, and – 24.4, respectively. The efficacy of quetiapine appears to be consistent across age groups.

IL/0099, subgroup analysis demonstrated that quetiapine was consistently efficacious, regardless of concomitant mood stabilizer treatment, gender, race, or age. Approximately 60% of subjects were treated with valproate, and 40% were treated with lithium. The distribution was quite similar within treatment groups. Quetiapine treatment was consistently efficacious across treatment groups. The LS mean difference in YMRS score between quetiapine and placebo was –2.9 for the lithium subgroup and –4.9 for the valproate subgroup. In this study, it does not appear that the efficacy of quetiapine was consistent with regard to the presence or absence of psychotic symptoms at baseline. For subjects with psychotic symptoms (N = 72), the LS mean difference between quetiapine and placebo was –9.0, favoring quetiapine. For subjects without psychotic symptoms at baseline (N = 98), the LS mean difference between treatment groups was zero. In Study IL/0099, 56% of subjects were men and 44% were women. For men, the estimated LS mean difference between quetiapine and placebo treatment was –6.3. The difference for women was –1.4. Thus, the quetiapine effect was consistent between genders. Descriptive statistics also suggest that quetiapine was consistently efficacious across racial groups [Caucasian {71%}, Black {19%}, and Latino {6.5%}]. The between-treatment differences were –4.0, –5.6, and –6.3, respectively. For the two age groups, 18-39 and 40-64, quetiapine was consistently efficacious. There were similar numbers of subjects in each age group, and the between-treatment differences were nearly identical.

VII. Integrated Review of Safety- Studies IL/0104, IL/0105, IL/0099, IL/0100

A. Statement of Safety Conclusions

Quetiapine treatment was reasonably safe and well tolerated as monotherapy and as adjunctive therapy to lithium or valproate. There were no new or unexpected findings with quetiapine treatment. In the four trials, 405 subjects were exposed to quetiapine and 411 were treated with placebo. The total quetiapine exposure was 49.3 patient-years. (Details about quetiapine exposures are discussed below in Section B). The types and frequency of safety assessments were appropriate for this indication, and they were adequate for detecting potential safety problems. (Refer to Section C for details). There were 3 deaths in the trials (one in the quetiapine groups and two in the placebo groups). The death in the quetiapine group was not related to quetiapine treatment. There were fewer serious adverse events in the quetiapine groups (17) than in the placebo groups (25). Only two serious adverse events were likely related to quetiapine treatment (syncope and orthostatic hypotension). Fewer subjects in the quetiapine groups discontinued due to adverse events (24) than in the placebo groups (31). In the quetiapine groups, a significant number of adverse events leading to discontinuation were very likely related to quetiapine treatment. These adverse events were rash, seizure, asthenia, somnolence, dizziness, nausea, and various extrapyramidal symptoms (tremor, dysarthria, hypokinesia, and extrapyramidal disorder).

In the monotherapy trials, the most common adverse events associated with quetiapine treatment (versus placebo) were somnolence (16% vs. 4%), dry mouth (16% vs. 3%), extrapyramidal symptoms (13% vs. 13%), weight gain (9% vs. 2%), dizziness (7% vs. 3%), headache (6% vs. 4%), asthenia (5% vs. 2%), orthostatic hypotension (4% vs. 2%), constipation (4% vs. 1%), and fever (3% vs. 1%). As illustrated above, the proportion of quetiapine-treated subjects reporting EPS was similar to that in the placebo group. In the adjunctive therapy trials, the most commonly reported adverse events were similar to those in the monotherapy trial; although, there were higher reporting rates of somnolence, tremor, and EPS. These findings are very likely related to concomitant treatment with either lithium or valproate. The commonly reported adverse events in the adjunctive trials were somnolence (34% vs. 10%), extrapyramidal symptoms (21% vs. 19%), headache (17% vs. 13%), constipation (10% vs. 5%), asthenia (10% vs. 4%), dizziness (9% vs. 6%), abdominal pain (7% vs. 4%), orthostatic hypotension (7% vs. 2%), nausea (6% vs. 6%), weight gain (6% vs. 3%), and pharyngitis (6% vs. 3%). In both treatment groups, a considerable proportion of cases of EPS were due to tremor.

The safety review also focused on specific adverse events and safety findings of particular interest. As noted above, the proportion of subjects reporting EPS was very similar in the quetiapine and placebo groups for both the monotherapy and adjunctive therapy studies. There were no significant differences between treatment groups in mean glucose concentrations. The mean glucose concentration in the quetiapine groups did not change significantly. Only 6 subjects in the trials developed elevated glucose concentrations (4 in the quetiapine group and 2 in the placebo group). Quetiapine treatment was associated with weight gain in the trials (+1.8 kg in the monotherapy trials and +2.97 kg in the adjunctive trials. The mean thyroxine concentrations decreased significantly (15% to 21%) in the trials, and the mean TSH concentration increased in the adjunctive therapy trials. However, relatively few subjects had abnormal thyroid function test results. Few subjects in the trials reported adverse events possibly related to abnormal serum prolactin concentration. Several subjects had elevated prolactin concentrations. However, the mean serum prolactin concentration decreased in both groups,

probably due to the fact that the majority of subjects had been treated with typical antipsychotics before the trial began. Neutropenia occurred in 2 subjects in the quetiapine group and in none of the placebo group. There was one adverse event of cataract reported. There were no clinically significant findings pertaining to vital sign values, and there were no significant electrocardiogram findings.

B. Description of Patient Exposure to Quetiapine

During the four trials, 404 subjects were exposed to quetiapine for a maximal duration of between 21 and 84 days, depending on the individual study. The cumulative quetiapine exposure was 49.3 patient-years. For the 21-day phases of the 4 trials, the quetiapine exposure was 20.2 patient-years. In the monotherapy trials, 208 subjects were exposed to quetiapine for a total exposure of 35.7 patient-years. In the adjunctive therapy trials, 196 subjects were treated with quetiapine for a total exposure of 13.6 patient-years.

In Study IL/0104, the mean daily dose of quetiapine was 526 mg/day, and the mean cumulative dose per subject was 30,329 mg. In Study IL/0105, the mean daily dose of quetiapine was 608 mg/day, and the mean cumulative dose of quetiapine per subject was 43,473 mg. In Study IL/0099, the median daily dose during the last week of treatment was 500 mg/day, and the mean cumulative dose per subject was 7,952 mg (for this 21-day study). In Study IL/0100, the median daily dose during the last week of treatment was 455 mg, and the mean cumulative dose per subject was 15,229 mg.

C. Adequacy of Safety Testing in All Trials

The types and frequency of safety assessments was appropriate for these trials. There was particular focus on potential adverse events that have been reported with quetiapine treatment. The safety assessment method was appropriate for identifying potential safety concerns that had not been associated with quetiapine treatment.

Safety Assessments and Schedule of Assessments:

1. Adverse event reporting- at screening and Days 1, 4, 7, 14, 21, 28, 42, 56, 70, and 84.
2. Modified Simpson-Angus Scale- on Days 1, 4, 7, 14, 21, 28, 42, 56, 70, and 84.
3. Barnes Akathisia Rating Scale – on Days 1, 4, 7, 14, 21, 28, 42, 56, 70, and 84.
4. Serum pregnancy test- at screening and on Day 84
5. Physical examination- at screening and on Day 84
6. Hematological, clinical chemistry testing- on Days 1 and 84
7. 12- lead electrocardiogram- on Days 1 and 84
8. Thyroid function tests- on Days 1 and 84
9. Vital signs and weight- at screening and Days 1, 4, 7, 14, 21, 28, 42, 56, 70, and 84
10. Prior and concurrent medication record- at screening and Days 1, 4, 7, 14, 21, 28, 42, 56, 70, and 84

D. Specific Findings of the Safety Analysis

Table. Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events

	QTP N = 405	PLA N = 401

Deaths	1 (0.2%)	2 (0.5%)
Serious Adverse Events	17 (4%)	25 (6%)
Discontinuations due to Adverse Events	24 (6%)	31 (8%)

D.1. Deaths in the Trials

There were no deaths during Study IL/0104; however, there were two deaths during Study IL/0105. A 68-year-old Asian woman treated with quetiapine 800 mg/day died of cardiac arrest and renal failure two days after withdrawing from the study (Day 30). The subject had a history of diabetes mellitus and hypertension. She had been treated with numerous medications for these conditions. At baseline, her ECG intervals and vital signs were normal. The subject had dizziness and "speech disorder" early in the trial. Twenty days later, she developed fever and diarrhea, and she was treated with intravenous fluids. Blood glucose and blood pressure were in the normal range. The subjected reported feeling dizzy and weak shortly before she had cardio-pulmonary arrest. It is unlikely that the death was related to quetiapine treatment; however, it is possible that there was a relationship, since the subject was dizzy and hypotensive during the apparent onset of the acute event. A 53-year-old Caucasian man (in the placebo group) died from complications of a perforated gastric ulcer, peritonitis, and hypovolemia. There were no deaths during study IL/0099. In Study IL/0100, one subject (treated with placebo and lithium) died due to complications of a cerebrovascular accident and cardiac valvular disease.

D.2. Serious Adverse Events

In the monotherapy trials, there were 4 serious adverse events in the quetiapine group and 13 in the placebo group. In the quetiapine group, the events were cardiac arrest (described above), syncope, atrial fibrillation, and abscess (anal), all of which led to discontinuation from the trial. The case of syncope was probably related to quetiapine treatment. A 68-year-old woman, (treated with quetiapine 150 mg/day), lost consciousness while eating on Day 3 of treatment. She became pale and diaphoretic, and her blood pressure was undetectable. She regained consciousness upon being placed in the supine position. She was treated with glucose and potassium. An ECG and cardiac enzyme testing did not suggest that there was an acute cardiac event. The sponsor reports that she had recovered 2 hours after the event. The subject had a history of chronic bronchitis. It is not clear whether she had a history of cardiac or cardiovascular disease. Concomitant medications included theophylline, thiamine, pyridoxine, and ascorbic acid. No other details about her medical history are available. The subject had the last dose of study medication on Day 5, and she was discontinued from the study. The investigator judged that the event was related to the study treatment and resultant orthostatic hypotension. The events in the placebo group were gastric perforation and peritonitis, intentional injury, arm fracture, 4 cases of agitation, and one case each of delusions, hallucinations, insomnia, nervousness, and pneumonia.

In the adjunctive therapy trials, there were 13 serious adverse events in the quetiapine group and 15 serious adverse events in the placebo group. In the quetiapine group, there were 4 cases of depression, one overdose, one suicide attempt, orthostatic hypotension, agitation, myelitis, paranoia, personality disorder, abnormal thinking, and pneumonia. Of these cases, only orthostatic hypotension was likely related to quetiapine and/or mood stabilizer treatment. None of the cases of depression or suicidality appear to have been related to quetiapine treatment. The

SAE in the placebo group included depression, manic reaction, hallucination, agitation, leukopenia, and various medical problems that are not likely to have been related to study treatment.

D.3. Discontinuations Due to Adverse Events

In the monotherapy trials, there were 14 adverse events leading to discontinuation from the quetiapine group and 16 adverse events leading to discontinuation from the placebo group. The SAE cases have been described above. In the quetiapine group, the non-serious adverse events leading to discontinuation were rash, seizure, 3 cases of depression, asthenia, tremor, EPS, dysarthria, hypokinesia, and gastritis. The cases of rash, seizure, and EPS were likely related to quetiapine treatment. The case of rash developed on Day 8 of treatment. The rash was described as a 'skin eruption of total body.' Quetiapine treatment was discontinued within 2 days, and the subject was withdrawn from the study. The adverse event was considered by the investigator to be related to treatment with quetiapine. Details about the subject's outcome are unavailable. The seizure occurred on Day 8 of treatment in a 19-year-old Asian woman. The seizure was described as a generalized tonic clonic seizure. The patient recovered within 5 minutes, and no symptomatic treatment was given. The event was considered related to treatment with quetiapine (300mg/day), and the patient was withdrawn from the study. She had no history of seizures but had received recent treatment with olanzapine, trihexyphenidyl, diazepam, lorazepam, haloperidol and zolpidem before entry into the study. Lorazepam, trihexyphenidyl, ibuprofen and zolpidem had been taken concurrently with study treatment. In the placebo group, the non-serious events included 3 cases of depression and one case each of accidental injury, hostility, hypertension, vasodilatation, seizure and akathisia.

In the adjunctive therapy trials, there were 10 adverse events leading to discontinuation from the quetiapine group and 15 adverse events leading to discontinuation from the placebo group. Two subjects who discontinued from the quetiapine group had adverse events that were likely related to quetiapine treatment. One subject had severe nausea, and another subject discontinued due to somnolence, dizziness, and nausea. None of the other AE in the quetiapine group was likely related to quetiapine treatment. These events included agitation, paranoia, hostility, intentional injury, and manic reaction. In the placebo group, the adverse events leading to discontinuation were manic reaction, depression, agitation, hypertension, hostility, arrhythmia, abnormal ECG, diarrhea, rash, and pruritus.

D.4. Commonly Reported Adverse Events

In the monotherapy trials, the most common adverse events associated with quetiapine treatment (versus placebo) were somnolence (16% vs. 4%), dry mouth (16% vs. 3%), extrapyramidal symptoms (13% vs. 13%), weight gain (9% vs. 2%), dizziness (7% vs. 3%), headache (6% vs. 4%), asthenia (5% vs. 2%), orthostatic hypotension (4% vs. 2%), constipation (4% vs. 1%), and fever (3% vs. 1%). As illustrated above, the proportion of quetiapine-treated subjects reporting EPS was similar to that in the placebo group. In the adjunctive therapy trials, the most commonly reported adverse events were similar to those in the monotherapy trial; although, there were higher reporting rates of somnolence, tremor, and EPS. These findings are very likely related to concomitant treatment with either lithium or valproate. The commonly reported adverse events were somnolence (34% vs. 10%), extrapyramidal symptoms (21% vs.

19%), headache (17% vs. 13%), constipation (10% vs. 5%), asthenia (10% vs. 4%), dizziness (9% vs. 6%), abdominal pain (7% vs. 4%), orthostatic hypotension (7% vs. 2%), nausea (6% vs. 6%), weight gain (6% vs. 3%), and pharyngitis (6% vs. 3%). In both treatment groups, a considerable proportion of cases of EPS were due to tremor.

D.5. Adverse Events and Safety Findings of Particular Interest

Extrapyramidal Symptoms

In the monotherapy and adjunctive trials, the proportion of subjects reporting EPS was very similar in the quetiapine and placebo groups. In the monotherapy trials, the reporting percentage was 13% for each treatment group, and in the adjunctive trials, the proportion of quetiapine-treated subjects was 21%, compared to 20% of the placebo group. Many of the subjects with EPS reported having tremor. In decreasing order of frequency, the most common types of EPS in the monotherapy trials were 'extrapyramidal disorder,' akathisia, and dysarthria, followed by hypertonia, bradykinesia, and hypotonia. The pattern was somewhat different (as expected) in the adjunctive therapy trials. The most common types of EPS reported were tremor, akathisia, hypertonia, twitching, speech disorder, incoordination, 'extrapyramidal disorder,' and ataxia. The relatively low incidence of EPS in the trials is consistent with previous experience with quetiapine. The low use of anticholinergic medications during the trials parallels the adverse events findings

Glucose Metabolism

In these studies, there were no significant differences between treatment groups in relevant parameters, with the exception of weight gain. In the 12-week monotherapy studies, there were 21 (10%) subjects in the quetiapine group and 4 (2%) subjects in the placebo group who had adverse events potentially related to diabetes. In both groups, the majority of these events were weight gain (19 cases in the quetiapine group and 3 cases in the placebo group). The other adverse events in the quetiapine and placebo group were hyperglycemia (1 vs. 0), polyuria (1 vs. 2), thirst (3 vs. 0), and urinary frequency (2 vs. 0). The mean random glucose concentrations decreased in both treatment groups at the end of the 21-day study. In quetiapine group, the change in mean glucose concentration was −3.4 mg/dL. The change in the placebo group was −4.0 mg/dL. There were relatively few subjects in the quetiapine group (2) who developed clinically significant elevations in glucose concentration. There were none in the placebo group.

In the adjunctive therapy studies, there were no significant differences between treatment groups in relevant parameters, with the exception of weight gain. There were 15 (8%) subjects in the quetiapine group and 6 (3%) subjects in the placebo group who had adverse events potentially related to diabetes. As in the monotherapy studies, the majority of these events were weight gain (12 in the quetiapine group and 5 in the placebo group). The other adverse events in the quetiapine and placebo group were diabetes mellitus (1 vs. 0), hyperglycemia (1 vs. 1), polyuria (1 vs. 0), thirst (1 vs. 0), and urinary frequency (1 vs. 0). In the quetiapine group, the change in mean random glucose concentration (+0.64 mg/dL) was less than that in the placebo group (+2.7

mg/dL). Two subjects in the quetiapine group and two subjects in the placebo group had elevations in glucose concentration which were potentially clinically significant.

Weight Gain

Quetiapine treatment was associated with weight gain in the trials. In the monotherapy trials, the mean weight increased in the quetiapine group from baseline to endpoint (+1.8 kg). In the placebo group, the mean weight decreased (− 0.15) kg. In the quetiapine group, 21% of subjects had a ≥ 7% increase in weight (compared to 7% in the placebo group). In the adjunctive therapy trials, there was a greater change in mean weight in the quetiapine group (+ 2.97 kg) than in the placebo group (0.27 kg), regardless of which mood stabilizer was used. In the quetiapine group, 13% of subjects had a ≥ 7% increase in weight (compared to 4% of the placebo group). As expected, increases in mean body mass index paralleled the increases in mean weight in the quetiapine group.

Thyroid Function

There were substantial decreases in thyroid hormone concentrations during the trials, and there were substantial increases in TSH concentrations in the adjunctive therapy trials. Within the quetiapine group in the 84-day monotherapy trials, the mean free thyroxine concentration decreased by 16%, and the mean total thyroxine decreased by 20%. In the placebo group, the mean free and total thyroxine concentrations increased by 2.5% and 4.5%, respectively. The mean TSH increased by only 1.2% in the quetiapine group. In the placebo group, the mean TSH concentration decreased by 1.2%. In the quetiapine group, 42% of subjects had a ≥20% decrease in free thyroxine concentration (compared to 12% of the placebo group), and 50% of the quetiapine group had a >20% decrease in total thyroxine concentration (compared to 11% of the placebo group). The increase in mean TSH concentration for subjects with a ≥20% decrease in free or total thyroxine level was slightly higher in the quetiapine group than in the placebo group, but the change was similar to that of subjects in both groups who did not.

In the quetiapine group, none of the subjects had a low free thyroxine level which was in the potentially clinically significant range, but 2% had low total thyroxine levels which were in the potentially clinically significant range. There were no individual abnormalities in thyroxine levels for the placebo group. The TSH level was significantly elevated for 0.5% of the quetiapine group and 2.2% of the placebo group. Thus, in these 12-week trials, it appears that the significant decrease in thyroxine levels was not accompanied by a significant increase in TSH concentration.

In the adjunctive therapy trials, the mean thyroxine concentrations decreased significantly in the quetiapine group. The mean free thyroxine level decreased by 15%, (compared to 3% in the placebo group), and the mean total thyroxine decreased by 21%, (compared to an increase of 2.3% in the placebo group). In contrast to the monotherapy trials, the mean TSH concentration increased by 56% in the quetiapine group and 37% in the placebo group. Generally, the changes in thyroxine and TSH levels were more pronounced within the subgroup treated with lithium, compared to the subgroup treated with valproate; however, the association of quetiapine treatment with alterations of thyroid function was consistent. In the quetiapine group, 45% of subjects had a ≥20% decrease in free thyroxine concentration (compared to 21% of the placebo

group), and 62% of the quetiapine group had a ≥20% decrease in total thyroxine concentration (compared to 13% of the placebo group). The increase in mean TSH concentration for subjects with a ≥20% decrease in free and total thyroxine level was slightly higher in the quetiapine group than in the placebo group (62%), but the change was similar to that of subjects in both groups who did not.

In the quetiapine group, 8% of the subjects had a low free thyroxine level that was in the potentially clinically significant range, and 15% had low total thyroxine levels that were in the potentially clinically significant range. (The proportions in the placebo group were 0% and 2.5%, respectively). The TSH level was significantly elevated for 14% of the quetiapine group and 8% of the placebo group. In a significant number of cases, a significant decrease in thyroxine concentration was accompanied by a significant increase in TSH concentration. cases. Three subjects in the quetiapine group and one in the placebo group had both a clinically significant reduction of free thyroxine concentration and a clinically significant elevation in TSH concentration. Furthermore, 5 subjects in the quetiapine group and one in the placebo group had both a clinically significant reduction of total thyroxine concentration and a clinically significant elevation in TSH concentration. In the quetiapine group, 8% of subjects with a ≥20% decrease in free thyroxine also had a significant elevation of TSH concentration (compared to 3% of the placebo group). Similarly, 12% of subjects with a ≥20% decrease in total thyroxine also had a significant elevation of TSH concentration (compared to 1.4% of the placebo group).

Labeling for quetiapine contains a section about the possible risk of hypothyroidism during the course of treatment with quetiapine. Under **PRECAUTIONS, General**, there is an entry for 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 0.4% (10/2386) of SEROQUEL patients did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment."

Prolactin Concentration and Related Adverse Events

Few subjects in the monotherapy trials reported adverse events that were possibly related to abnormal serum prolactin concentration. Amenorrhea was reported by 0.5% of the quetiapine group and none of the subjects in the placebo group. There were no reports of galactorrhea. In the adjunctive therapy trials, a small number of subjects reported adverse events that were possibly related to abnormalities in prolactin levels. In the quetiapine group, decreased libido, galactorrhea, impotence, breast pain, and dysmenorrhea were reported by 0.5%, 1%, 1%, 0.5%, and 0.5% of subjects, respectively. None of these adverse events were reported by subjects in the placebo group.

At baseline in the monotherapy studies, the mean serum prolactin level was elevated, paralleling the high proportion of subjects who were treated with typical antipsychotic medications before

study treatment began. During the trials, there was a substantial decrease in mean prolactin concentration in both the quetiapine and placebo group. (In IL/0104, the change in mean prolactin concentration was –11.9 ug/L in the quetiapine group and –9.5 ug/L in the placebo group). In both treatment groups, a significant proportion of male and female subjects had increases in prolactin concentration which were potentially clinically significant. In the quetiapine group, 7% of women had a prolactin level >30 ug/L, and 17% of men had a prolactin level >20 ug/L. In the placebo group, the respective proportions were 16% and 11%. Serum prolactin concentrations were not measured in the adjunctive therapy trials.

Neutropenia

In monotherapy IL/0104, there were two cases of neutropenia in subjects treated with quetiapine. (No subjects in the placebo group developed neutropenia). One subject (0374/0875) had a significantly low absolute neutrophil count (ANC) of 0.4 x10^9/L on Day 21. The baseline WBC was 7.7x 10^9/L; there was no baseline measurement of ANC. During the trial, there were no clinical adverse events reported for this subject who discontinued due to deterioration of his psychiatric condition. Follow-up information was not provided. The subject had also been treated with glibenclamise, which had been associated with transient neutropenia. The other subject (0374/0871) had an ANC of 1.0 x 10^9/L on Day 19, compared to 3.2 x 10^9/L at baseline. This subject had the adverse events, infection with pharyngitis, which lasted for 4 days. The subject was withdrawn from the study, because he was lost to follow-up. No additional information is available regarding this subject. There were no cases of neutropenia or agranulocytosis in any of the other three trials.

Depression

The adverse event, "depression" was defined as the occurrence of a MADRS score of $\geq$18 during two consecutive visits, with an increase from baseline of $\geq$ 4, or a MADRS score $\geq$18 at the final visit, with an increase from baseline $\geq$ 4. In all four trials, the proportion of subjects with depression was low in both the quetiapine and placebo groups. It does not appear that quetiapine treatment resulted in depressive symptoms in most of the cases. In the monotherapy studies, the adverse event, depression was reported for 3.8% of the quetiapine group and 2.5% of the placebo group. Most of these events were considered mild and were likely not related to treatment with quetiapine. One case of depression was considered moderate and likely related to quetiapine treatment (by the investigator). The subject discontinued from the study. In the adjunctive therapy trials, 3% of the quetiapine group and 2% of the placebo group had the adverse event, depression. One percent (1%) of the quetiapine group and 0.5% of the placebo group made a suicide attempt (without completion). It is unlikely that the suicide attempts in the quetiapine group were related to quetiapine treatment.

Based on information from the case reports of depression, it is difficult to conclude whether or not the depressive symptoms were related to quetiapine treatment, for a number of reasons. Some of the relevant subjects had not been compliant with medication treatment, some had depressive symptoms at baseline, and some appeared to have had significant psychosocial

stressors during the period in which they experienced depressive symptoms. However, it is conceivable that quetiapine treatment may have caused or exacerbated depressive symptoms in some cases. It is also possible that some of the subjects experiencing depression were also experiencing asthenia (5.3% of the quetiapine group, compared to 2% of the placebo group) and/or EPS which may have been interpreted as depressive symptoms.

Cataracts

In trial IL/0099, there was one adverse event of cataract reported in a 50 year-old man (subject 0037/1139) who had previously been treated with divalproex and was randomly assigned to quetiapine. At the screening physical exam, there were no cataract detected during ophthalmoscopic exam by a non-ophthalmologist. The subject was treated with quetiapine 600 mg per day, and he continued treatment with valproate 2000 mg/day. On Day 20, the subject had a final physical examination by another practitioner, who noted bilateral cataracts on ophthalmoscopic examination. The examiner did not note the extent or location of the cataracts, and it was not noted whether visual acuity was affected. No slit lamp examinations were performed. The subject had a past medical history of chronic back pain, chronic obstructive pulmonary disease, psoriasis, and intermittent lower extremity edema of unknown etiology. Medications on admission included diclofenac, salbutamol, zoleplon, olanzapine, and valproate. Prior psychotropic medications included Effexor, Wellbutrin, Zoloft, imipramine, Neurontin, trazodone, and Trileptal. It was not known whether the patient had been treated with steroids for the pulmonary disease, back pain, or psoriasis. Risk factors for cataracts include a 46 pack-year smoking history. The event was determined by the investigator to be mild, not serious, and not drug-related. The subject was not withdrawn from the study. Follow-up revealed that the subject continued to be treated with quetiapine, but had no further ophthalmoscopic examinations.

D.6. Vital Signs

In the monotherapy and adjunctive therapy trials, there were no significant changes in mean vital sign parameters in either treatment group. For most vital sign parameters in the monotherapy trials, there were no significant differences between treatment groups in the proportion of subjects who had potentially clinically significant changes. However, the quetiapine group had a higher proportion of subjects (12%, compared to 5% in the placebo group) who had a $\geq$15 bpm increase in supine pulse. There were no corresponding significant findings for changes in standing pulse, standing diastolic blood pressure, or standing systolic blood pressure. In the adjunctive therapy trials, there were no significant differences between treatment groups in the proportion of subjects who had potentially clinically significant changes.

D.7. Electrocardiogram

In the monotherapy and adjunctive therapy trials, there were no significant changes in mean ECG parameters in either treatment group, and there were no significant differences between groups. There was no significant change in mean QT interval for the quetiapine group. decreased by 3 msec, and the QTc decreased by 2 msec. In the monotherapy trials, 1% of the quetiapine group and 3% of the placebo group developed a QTc >450 msec. In the adjunctive therapy trials, 2% of subjects in each treatment group developed a QTc interval >450 msec.

D.8. Clinical Laboratory Findings (other than glucose, prolactin, and thyroid function)

Hematological Parameters
For all trials, there were no significant changes in mean WBC, neutrophil count, or other hematological parameters, and there were no significant differences between the quetiapine and placebo groups. As noted above, there were two cases of neutropenia in trial IL/0104 (ANC $<1.0 \times 10^9$). In the monotherapy trials, five subjects (2.7%) in the quetiapine group and one subject (0.6%) in the placebo group had a neutrophil count $\leq 1.5 \times 10^9$. Six percent (6%) of the quetiapine group and 1% of the placebo group had eosinophilia. In the adjunctive therapy trials, one subject (0.6%) in the quetiapine group and none in the placebo group had a neutrophil count $\leq 1.5 \times 10^9$. Eosinophilia was detected in 2.6% of the quetiapine group and 1.2% of the placebo group.

Clinical Chemistry Parameters (Hepatic Function, Renal Function, and Electrolytes)
In all trials, there were no significant changes in mean clinical chemistry values (other than thyroid function tests and prolactin concentration). In the quetiapine groups, there was no increase in mean LFT or renal function test values, and there were no significant changes in mean electrolyte values. There were no significant differences in these values between the quetiapine and placebo groups. In the monotherapy trials, 0.5% of subjects in the quetiapine group had a clinically significant elevation of AST (compared to 1.1% of the placebo group), and none of the quetiapine group had a clinically significant elevation of ALT (compared to 1.1% of the placebo group). In the adjunctive therapy trials, 0.6% of the quetiapine group and none of the placebo group had clinically significant elevation of AST. Similarly, 0.6% of the quetiapine group and none of the placebo group had a clinically significant elevation of ALT.
For all of the trials, no subject in either treatment group had a clinically significant elevation of BUN or creatinine. Only a small number in subjects in each treatment group had abnormal electrolyte values that were potentially clinically significant. The proportion of such subjects was very similar between treatment groups.

XVI. Quetiapine Dosing, Regimen, and Administration Issues

The dosing and administration regimen proposed by the sponsor is reasonable, based on the efficacy and safety results of the mania trials and based on previous experience treating schizophrenic patients. For the treatment of acute mania, the sponsor recommends initiating quetiapine treatment at 100 mg/day, divided BID, increasing by 100 mg per day to 400 mg/day on Day 4. The clinician can make further adjustments up to 800 mg/day by Day 6, in increments no greater than 200 mg/day. The sponsor states that the majority of subjects who 'responded' did so in the range of 400-[ ]mg. However, these were flexible-dose studies. Thus one cannot conclude that the trials established either a minimal effective dose or a dose-response relation-

ship. It is possible that at least some subjects would have improved with lower doses, if the titration schedule had been more gradual.

For two reasons, I recommend that the sponsor consider altering the suggested regimen such that quetiapine would be administered as either a [ ] [ ]. Daytime somnolence was one of the most common adverse events for subjects treated with quetiapine (16% of subjects in the monotherapy studies and 26% of subjects in the adjunctive trials). Furthermore, insomnia (an important feature of acute mania) was reported by 14% of subjects treated with quetiapine in the monotherapy trial. (Only 6% of quetiapine-treated subjects reported insomnia in the adjunctive trials). [ ] [ ] In addition, patients might be more likely to adhere to treatment with quetiapine. Perhaps the sponsor recommends an evenly divided BID dosing due to the relatively short mean terminal half-life of quetiapine (approximately 6 hours). However, it is possible that efficacy would not be compromised by altering the suggested dosing regimen.

Age. Oral clearance of quetiapine can be reduced by 40% in elderly patients (≥65 years) compared to young patients. Dosing adjustment may be necessary in this population.

Renal Impairment. Patients with severe renal impairment (creatinine clearance = 10–30 mL/min/1.73 m^2) have a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2) [ ] Plasma quetiapine concentrations in 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 can have a 30% lower mean oral clearance of quetiapine than normal subjects. In hepatically impaired patients, AUC and Cmax can be three-fold those observed in healthy subjects. Since the liver extensively metabolizes quetiapine, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment [ ] be necessary.

XVII. Quetiapine Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation and

Evaluation of Evidence for Age, Race, or Ethnicity Effects On Safety or Efficacy

The sponsor appears to have thoroughly analyzed any possible effect of gender on efficacy and safety results. Quetiapine treatment was consistently efficacious, regardless of gender, race, ethnicity, geographic region, or age. The sponsor provided descriptive statistics for the estimated treatment effect within these relevant subgroups. The proportion of men and women in the studies was very similar. In the four studies, there were 479 (49%) men and 490 (51%) women. The proportion of men and women treated with quetiapine were also very similar. The

monotherapy studies were conducted at numerous international sites throughout Europe, Asia, and South America, and one of the adjunctive therapy studies was conducted at numerous international sites in Europe, Canada, India, and South Africa. The other adjunctive study was conducted in the U.S. As a result, there was considerable ethnic and racial diversity among the trials. In the monotherapy trials, 63% of subjects were Caucasian, none were Black, 34% were Asian, 2% were Latino, and 1% was 'Mixed.' The various subgroups were evenly distributed among treatment groups. In the adjunctive trials, 72% of subjects were Caucasian, 10% were Black, 3% were Latino, 3% were Asian, 3% were Mixed, and 9% were 'Other.' The subgroups were evenly distributed between treatment groups. There were few subjects in the trials ≥ 65 years of age. Only 5% of the monotherapy population and 3% of the adjunctive therapy population were ≥ 65 years of age, but quetiapine appeared to be efficacious in this age group.

C. Evaluation of Pediatric Program

Quetiapine treatment has not been studied in children or adolescents. The Division will discuss potential plans for relevant studies.

D. Comments on Data Available or Needed in Other Populations as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

The sponsor has provided substantial data regarding the use of quetiapine in patients with renal or hepatic impairment. While there are some data pertaining to the use of quetiapine during pregnancy, additional information would be extremely once it becomes available. It is likely that quetiapine would be used in some pregnant women with acute mania.

XVIII. Conclusions and Recommendations

A. Conclusions

The results of two studies demonstrated that quetiapine, as monotherapy, was efficacious in the acute treatment (for 21 days) of adult patients diagnosed with Bipolar I Disorder, Manic Phase. The treatment effect was meaningful clinically. Similarly, a third study demonstrated that quetiapine, as adjunctive therapy to the mood stabilizers lithium or valproate, was efficacious in the acute treatment (for 21 days) of adult patients diagnosed with Bipolar I Disorder, Manic Phase. The treatment effect was meaningful clinically. Another adjunctive therapy study did not demonstrate the efficacy of quetiapine plus a mood stabilizer in the acute treatment of mania.

In these 4 trials, treatment with quetiapine was reasonably safe and well tolerated. No new or unexpected safety findings were identified during the mania trials.

However, based on information from the sponsor's Periodic Safety Update Report, it appears likely that the Division and the sponsor will need to discuss safety issues such as sequelae of quetiapine ovedose, the possible association between quetiapine treatment and neutropenia and agranulocytosis, and other currently unlabelled serious adverse events including Stevens Johnson Syndrome, exfoliative dermatitis, anaphylaxis, and [redacted] (refer to Recommendations section below).

B. Recommendations

Given the efficacy results and safety findings of the trials under review, I recommend that the Division take approvable actions for quetiapine (both as monotherapy and as adjunctive therapy to mood stabilizers) in the treatment of adult patients with a diagnosis of Bipolar I Disorder, Manic or Mixed-Manic Phase, with or without Psychotic features.

The Division will discuss with the sponsor potential changes in labeling for quetiapine. Based on the findings from the Periodic Safety Update Report, I recommend that we consider including the following potential adverse events in labeling for quetiapine:

1. Possible sequelae of quetiapine overdose (death, coma, seizure, [ ], serious cardiac events).
2. Neutropenia, agranulocytosis
3. Stevens Johnson Syndrome
4. Anaphylactic reaction
5. [ ]
6. Rhabdomyolysis
7. [ ]
8. [ ]
9. Hyponatremia/SIADH

XIX. Appendix

Investigators and Sites:

Name and address	Trial No / Center No	Number of patients
David Brown MD Community Clinical Research, Inc. 4411 Medical Parkway Austin, TX 78756	5077IL/0099 Center 02	7 randomized
John Crayton MD Hines VAMC Building #228 Room 1072C 5th and Roosevelt Avenues Hines IL 60141	5077IL/0099 Center 03	4 randomized
Joseph McEvoy John Umstead Hospital 1003 12th Street Bldg 32 Butner, NC 27509	5077IL/0099 Center 06	9 randomized
Mohammid Bari Synergy Clinical Research Inst. 450 Fourth Avenue Suite 409 Chula Vista, CA 91910	5077IL/0099 Center 07	18 randomized
William Coryell MD University of Iowa College of Medicine, Psychiatry Research 2-205 MEB Iowa City, IA 52242-1000	5077IL/0099 Center 08	3 randomized

Name and address	Trial No / Center No	Number of patients
Louis Fabre MD Fabre Research Clinic, Inc. 5503 Crawford Houston, TX 77004	5077IL/0099 Center 09	3 randomized
Michael Lesem MD Claghorn-Lesem Research Clinic 6750 West Loop South Suite 1050 Bellaire, TX 77401	5077IL/0099 Center 11	12 randomized
Charles Merideth MD Affiliated Research Institiute 8989 Rio San Diego Drive Suite 350 San Diego, CA 92108	5077IL/0099 Center 12	4 randomized
Samuel C. Risch Medical Univ. of Southern Carolina, IOP 67 Presidents Street Room 502 North, PO Box 250861 Charleston, SC 29425-0742	5077IL/0099 Center 15	2 randomized
Joyce Small MD Larue D. Carter Memorial Hospital 2601 Cold Spring Road Indianapolis, IN 46222-2202	5077IL/0099 Center 16	4 randomized

Name and address	Trial No / Center No	Number of patients
Richard Weisler MD 900 Ridgefield Road Suite 320 Raleigh, NC 27609	5077IL/0099 Center 18	5 randomized
Michael Plopper MD Sharp Mesa Vista Hospital 7850 Vista Hill Avenue San Diego, CA 92123	5077IL/0099 Center 19	5 randomized
Joachim Raese MD Dr. Raese and Associates 5887 Brockton Avenue Suite A Riverside, CA 92506	5077IL/0099 Center 20	6 randomized
Robert T. Segraves MD, PhD Metro Health Medical Center Department of Psychiatry 2500 Metro Health Drive Cleveland, OH 44109	5077IL/0099 Center 21	2 randomized
Craig Wronski DO Himasiri DeSilva MD Affiliated Research Institute 801 N. Tustin Ave. Suite 600 Santa Ana, CA 92705	5077IL/0099 Center 22	13 randomized
Kathleen Toups MD Bay Area Research Institute 2123 Ygnacio Valley Road Suite K 200 Walnut Creek, CA 94598	5077IL/0099 Center 23	1 randomized

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Kenneth Sokolski Advanced Behavioral Research Institute 1735 West Romneya Anaheim, CA 92801	5077IL/0099 Center 24	11 randomized
Claudia Baldassano MD Friends Hospital 4641 Roosevelt Blvd Philadelphia, PA 19124-2399	5077IL/0099 Center 26	6 randomized
Lori Davis MD VA Medical Center 3701 Loop Road East Tuscalossa, AL 35404	5077IL/0099 Center 29	5 randomized
Andrew Cutler MD 807 West Morse Blvd St 101 Winter Park, FL 32789	5077IL/0099 Center 31	7 randomized
James C-Y Chou Bellevue Hospital Center Room 20 West 13A Dept of Psychiatry 462 1st Avenue New York, NY 10016	5077IL/0099 Center 32	8 randomized
Louise Beckett MD IPS Research Company 1211 North Shartel #407 Oklahoma City, OK 73103	5077IL/0099 Center 34	10 randomized
Ronald Brenner MD NeuroBehavioral Research Inc. 371 Central Avenue Lawrence, NY 11559	5077IL/0099 Center 36	7 randomized
David Feifel UCSD Medical Center 200 West Arbor San Diego, CA 92103	5077IL/0099 Center 37	8 randomized
Arman Goenjian 4510 East Pacific Coast Highway Suite 120 Long Beach, CA 90806	5077IL/0099 Center 38	12 randomized
William Privitera MD Future Search Trials 4200 Marathon Blvd. #200 Austin, TX 78756	5077IL/0099 Center 39	10 randomized
Anantha Shekhar Behavioral Care C-4 Methodist Hospital 1701 North Capitol Avenue Indianapolis, IN 46202	5077IL/0099 Center 42	4 randomized
M. Azfar Malik MD Psych Care Consultants 621 S. New Ballas Road Tower A, Suite 584 St. Louis, MO 63141	5077IL/0099 Center 43	5 randomized

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Dr. Eleni Palazidou Department of Psychiatry The Royal London Hospital St. Clement's 2A Bow Road London E3 4LL UK	5077IL/0100 Center 02	2 randomized
Dr. Michael Isaac Ladywell Building Lewisham Hospital Lewisham High Street London SE13 UK	5077IL/0100 Center 04	1 randomized
Dr. Alan Ogilvie King's Lynn & Wisbech Hospital's NHS Trust Queen Elizabeth Hospital Gayton Road King's Lynn PE30 4ET UK	5077IL/0100 Center 07	2 randomized
Dr. Martin Stefan Mental Health Services Addenbrooke's NHS Trust Fulbourn Hospital Cambridge CB1 5EF UK	5077IL/0100 Center 09	1 randomized
Prof. Joseph Peuskens Universitair Centrum Sint- Jozef Leuvensesteenweg 517 3070 Kortenberg Belgium	5077IL/0100 Center 31	1 randomized

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Prof. Arlette Seghers Cliniques Universitaires Saint-Luc, Service de psychopatologie Avenue Hippocrate 10 1200 Bruxelles Belgium	5077IL/0100 Center 32	1 randomized
Dr. André Roch De Nayer Hôpital Ste-Thérèse Rue Trieu Kaisin 134 6061 Montignies s/Sambre Belgum	5077IL/0100 Center 35	5 randomized
Dr. Laksmi Yatham Mood Disorders Clinical Research Unit Dept. of Psychiatry University of British Columbia, Vancouver, British Columbia Canada	5077IL/0100 Center 41	12 randomized
Dr. Arun Ravindran Royal Ottawa Health Care Group Room 2053, 1145 Carling Avenue, Ottawa, ON K1Z 7K4 Canada	5077IL/0100 Center 42	3 randomized

Dr. GlendaMcQueen McMaster University, 4N 77A Medical Center 1200 Main Street West Hamilton, Ontario Canada	5077IL/0100 Center 44	1 randomized
Dr. Jean Leblanc University of Monireal, Suite 505, Clinique des maladois affective Clinique Bolis-de Bologne, Montreal, PQ, H3M 3A9 Canada	5077IL/0100 Center 45	7 randomized
Dr. Philippe Baruch Ctr Hospital University Quebec-Enfant Jesus 1401 18e, Quebec, QC G1J 1ZA Canada	5077IL/0100 Center 46	4 randomized
Dr. Serge Beaulieu Department of Psychiatry Director affective Disorders Clinic, Douglas Hospital & Douglas Hospital Research Center 6875 La sale Blvd, Verdun Province de Quebec H4H 1R3 Canada	5077IL/0100 Center 47	4 randomized

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Dr. Yves Chaput Hospital Notre Dame,Montreal Dept of Pshyciatrie CHUM, Salle M-2209 A Pavillon Mailloux, 2eme 1560 rue Sherbrook East Montreal, PQ H2L 4M4 Canada	5077IL/0100 Center 48	2 randomized
Dr. Sunny Johnson Suite 202 Credit Valley Medical Arts Center 2000 Credit Rd Mississauga, Ontario L5M 4N4 Canada	5077IL/0100 Center 50	8 randomized
Dr. Pratap R. Chokka Grey Nuns Hospital Edmonton AB K6L 5X8 Canada	5077IL/0100 Center 51	2 randomized
Dr. Mary Connolly Rm 132 Eric Martin Pavillion, Royal Jubilee Hospital 2334 Trent St. Victoria BC V8R 4Z3	5077IL/0100 Center 52	6 randomized
Dr. Mihai Gheorghe Central Military Hospital Dept of Psychiatry, 88 M. Vilcanescu Street Bucharest Romania	5077IL/0100 Center 61	12 randomized

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Dr. Victoria Burtea Psychiatry and Neurology Hospital 18 M. Eminescu Street Brasov Romania	5077IL/0100 Center 62	12 randomized
Prof. Hans-Jürgen. Möller Klinik und Poliklinik für Psychatrie und Psychotherapie Klinikum der Universität München Dept of Psychiatry, University of Munich Nussbaumstrasse 7 D-80336 Munich Germany	5077IL/0100 Center 72	5 randomized
Prof. Peter Bräunig Klinikum Chemnitz gGmbH Akad. Lehrkrankenhaus der Universitaet Leipzig Klinik für Psychiatrie Verhaltensmedizin und Psychosomatik Dresdner Str.178 09131 Chemnitz Germany	5077IL/0100 Center 74	7 randomized
Prof. Ralf Uebelhack Klinik für Psychiatrie Universtätsklinikum Charité Schumannstr.20/21 10117 Berlin Germany	5077IL/0100 Center 75	6 randomized

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Prof. Robin A. Emsley Dept. Psychiatry Faculty of Medicine University of Stellenbosch. Po Box 19063 Tygerburg, Cape Town 7505 South Africa	5077IL/0100 Center 92	8 randomized
Dr. Robert Bothwell Valkenburg Hospital Education Centre Observatory 7935 Cape Town South Africa	5077IL/0100 Center 93	3 randomized
Prof. H.W.Pretorious Westkoppies Hospital Private Bag X113 Pretoria, 0001 South Africa	5077IL/0100 Center 94	9 randomized
Dr. Salumu Selemani Sterkfontein Hospital Private bag X2010 Krugersdorp 1740 South Africa	5077IL/0100 Center 95	28 randomized
Prof. S.T. Rataemane Oranje Hospital, Dept. of Psychiatry University of Orange Free State (OFS) P.O.Box 339, Bloemfontein 9300 South Africa	5077IL/0100 Center 96	2 randomized

Prof. Werner Felber Klinik und Poliklinik für Psychiatrie und Psychotherapie Universitätsklinikum Carl Gustav Carus, Haus 25 Fetscherstr. 74 01307 Dresden Germany	5077IL/0100 Center 76	3 randomized
Prof. Ekkehard Haen Psychiatrische Uniersitätsklinik Regensburg Bezirksklinikum Regensburg Universitätsstr.84 93053 Regensburg Germany	5077IL/0100 Center 77	1 randomized
Prof. Wolfgang Maier Klinik und Poliklinik für Psychiatrie und Psychotherapie Universitätsklinikum Bonn Sigmund-Freud-Str. 25 53105 Bonn Germany	5077IL/0100 Center 78	1 randomized
Prof. G.A.D Hart Tara Hospital Private Bag X7 Randburg 2125 South Africa	5077IL/0100 Center 91	1 randomized

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Dr. P.U. Ramjee Vista Clinic 135 Gerhard Street Centurion, 0046 South Africa	5077IL/0100 Center 97	4 randomized
Dr. F. Y Jeenah Chris Hani Baragwanath Hospital Block 85 Dept. of Psychiatry Old Potch Rd Johannesburg, 2013 South Africa	5077IL/0100 Center 98	1 randomized
Dr. Eduard Vieta Hospital Clinic Servei de Psiquiatria, Rosello 140 08036 Barcelona Spain	5077IL/0100 Center 101	3 randomized
Dr. Ana Gonzalez-Pinto Hospital Santiago Apostol Servicio de Psiquiatria Olaguibel 29 01004 Vitoria Spain	5077IL/0100 Center 102	2 randomized
Dr. Jesús Valle Hospital de la Princesa Servicio de Psiquiatria Diego de Leon 62 28006 Madrid Spain	5077IL/0100 Center 103	3 randomized
Dr. Gemma Garcia-Parés Corporacio Sanitaria Parc Tauli Servei de Psiquiatria Parc Tauli s/n 08208 Sabadell Spain	5077IL/0100 Center 104	1 randomized

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Dr Alfonso Rodriguez Institut Municipal de Psiquiatria D'Urgencia c/Germans Desvalls s/n 08035 Barcelona Spain	5077IL/0100 Center 106	5 randomized
Dr. Josep Gascon Hospital Mutua de Terrasa Plaza Dr. Robert, 5 8-14, 08221 Terrasa Barcelona Spain	5077IL/0100 Center 107	2 randomized
Dr. Eulalio Valmisa Hospital Universitario de Puerto Real Ctra Nacional IV, Km 665 11510 Puerto Real, Cadiz Spain	5077IL/0100 Center 108	1 randomized
Dr.Ivan Gerdjikov State Psychiatric Hospital 1282 Novi Iska, Sofia Bulgaria	5077IL/0100 Center 111	24 randomized
Dr. Shiv Gautam Superintendent Psychiatric Center Janta Colony, Jaipur 302 006 India	5077IL/0100 Center 121	5 randomized

Dr Alberto M. Bertoldi Clinica San Agustin Calle 55 n 763 (1900) La Plata Argentina	5077IL/0104 Center 211	6 randomized
Dr. Eduardo R. Merlo Clínica Privada de Psiquiatría San Juan, Calle 115 nº 231 (entre 36 y 37), (1900) La Plata, Argentina,	5077IL/0104 Center 212	4 randomized
Dr. María C. Castrillo Instituto Modelo San Jose, Belgrano 1443, (4600) Jujuy, Argentina.	5077IL/0104 Center 213	2 randomized
Dr Gerardo Carcía Bonetto Clinica Saint Michel Av Sagarada Familia 551 (5003) Córdoba Argentina	5077IL/0104 Center 214	6 randomized
Dr. Pedro R. Gargoloff Hospital Alejandro Korn, Calle 520 y 175, (1903) Melchor Romero, Argentina	5077IL/0104 Center 215	4 randomized
Dr. Carlos Morra Sanatorio Prof. Leon S. Morra S.A., Av. Sagrada Familia Esq. Nazaret, (5009) Córdoba, Argentina	5077IL/0104 Center 216	5 randomized

Dr. Jorge Nazar Hospital Carlos Pereyra, Ituzaingo 2835, (5500) Mendoza, Argentina	5077IL/0104 Center 217	2 randomized
Dr Jorge Marquet Clinica Avenida, Mitre 2222, (2000) Rosario, Argentina	5077IL/0104 Center 219	1 randomized
Dr Carlos Nunez Clinica San Jorge, Address: Av Eva Perón 1536, Lanús Este, Buenos Aries, Argentina	5077IL/0104 Center 220	4 randomized
Dr Ricardo Corral Hospital Municipal Jose P Borda, Ramon Carrillo 375, Buenos Aries, Argentina	5077IL/0104 Center 221	3 randomized
Dr Alberto Montchablon Hospital Braulio Moyano, Brandsen 2570, Buenos Aires, Argentina	5077IL/0104 Center 222	5 randomized
Prof. Shu Liang The sixth Hospital of college of Medicine, Beijing University Base for Drug Clinical Trial, No. 51 Huayuan Beilu, Haidian District, Beijing P.R., China 100083	5077IL/0104 Center 241	3 randomized
Prof. Weng Yongzhen Beijing An Ding Hospital affiliate of Capital University of Medical Sciences, De Sheng men wai Avenue, Beijing P. R., China 100088	5077IL/0104 Center 242	5 randomized

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Dr Veronica Larach Hospital Barros Luco/Trudeau Los Carpinteros 10182 Los Condes Santiago de Chile Chile	5077IL/0104 Center 251	10 randomized
Dr. Federico F. Bertran Vives Hospital Clinico Regional Valdivia, Servicio de Psiquiatria, Av. Simpson 850, Valdivia, Chile	5077IL/0104 Center 252	2 randomized
Dr Sergio Gloger Centro Neuropsiquiatrico de Santiago, Av. Portugal 128, Santiago, Chile	5077IL/0104 Center 253	2 randomized
Prof. V. Folnegovic-Smalc Psychiatric Hospital Vrapce, Universit Department of Psychiatry, Bolicka Cesta 32, 10090 Zagreb, Croatia	5077IL/0104 Center 261	15 randomized
Prof. Kocjian- Hercigonja University Hospital Dubravna, Department of Psychiatry and Psychotrauma, Avenia Gojka Suska 6, 10000 Zagreb, Croatia	5077IL/0104 Center 262	7 randomized
Dr. Mate Mihanovic Psychiatric Hospital Jankomir, Zagreb, Jankomir Str. 11, 10090 Zagreb- Susedgrad, Croatia	5077IL/0104 Center 263	2 randomized

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Dr. Ants Puusild Pärnu Hospital Psychiatric Clinic, Sääse tn. 3, EE 80012 Pärnu, Estonia	5077IL/0104 Center 271	13 randomized
Dr. Ljudmilla Väre Jämejala Psychiatric Hospital, EE 2900 Viljandi, Estonia	5077IL/0104 Center 272	4 randomized
Dr. Georgi Belotserkovski Ahtme Mental Hospital, 110 Ahtme Street, 31027 Kohtla-Jarve, Estonia	5077IL/0104 Center 273	3 randomized
Dr Irmansyah Department of Psychiatry Faculty of Medicine,University of Indonesia Jl Salemba 6 Jakarta,Indonesia	5077IL/0104 Center 282	2 randomized
Dr Soemarno Ws Department of Psychiatry Faculty of Medicine,Gajah Mada University,Sarjito Hospital,Jl Kesehatan No.1,Sekip Yogyakarta Indonesia	5077IL/0104 Center 283	1 randomized
Dr G.Pandu Setiawan Lawang Psychiatric Central Hospital Jl. A. Yani Lawang Malang Indonesia	5077IL/0104 Center 284	4 randomized
Dr Robert Reverger Department of Psychiatry Faculty of Medicine,Udayana University,Sanglah Hospital Denpasar Bali Indonesia	5077IL/0104 Center 285	3 randomized

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Prof Pranas Ulba Siauliai Psychiatric Hospital, M.K. Ciurliono 12, 5400 Siauliai , Lithuania	5077IL/0104 Center 321	7 randomized
Dr. Radavicius Vilnius Mental Health Centre, Vasaros str. 5, 2055 Vilnius, Lithuania	5077IL/0104 Center 322	18 randomized
Prof. Benjaminas Burba Kaunas Medical University Hospital, Department of Psychiatry, Eiveniu 2, LT-3000 Kaunas, Lithuania	5077IL/0104 Center 323	2 randomized
Prof Regina Satkeviciute ZIEGZDRAI Mental Hospital, Kaunas Region, LT-4313 Lithuania	5077IL/0104 Center 324	24 randomized
Prof. Emilis Subata Klaipeda Psychiatric Hospital, Bangu str. 6A, 5800 Klapeda , Lithuania	5077IL/0104 Center 325	8 randomized
Prof. R. Andrezina Riga Psihoneirologiska Slimnica, Psihiatrijas Katedra, Tavika iela 2, 1005 Riga, Latvia	5077IL/0104 Center 331	24 randomized
Dr. P. Ravelis Jelgava Psychiatric Hospital, Filozofu str.69, 3008 Jelgava, Latvia	5077IL/0104 Center 332	9 randomized
Dr. Imants Zeme Liepajas Psihoneirologiska Slimnica, Dartas Iela Str. 31, 3401 Liepaja, Latvia	5077IL/0104 Center 333	8 randomized

Dr. Efren Reyes National Center for Mental Health, 9 De Febrero St., Mandaluyong City, Philippines	5077IL/0104 Center 341	23 randomized
Dr. Anselmo Tronco University of the Philippines- Philippine General Hospital, Taft Avenue, Ermita, Manila, Philippines	5077IL/0104 Center 343	6 randomized
Dr. Vicente Cabuquit University of the East-Ramon Magsaysay Memorial Medical Center, Aurora Blvd., Quezon City, Philippines	5077IL/0104 Center 344	1 randomized
Dr. Henrietta Espanola West Visayas State University Hospital, Jaro, Iloilo City, Philippines	5077IL/0104 Center 345	2 randomized
Dr. Wlodzimierz Chrzanowski Medical Academy, Bialystok Klinika Chorob Psychicznych AMB16-070 Choroszcz/ k. Bialegostoku, Poland	5077IL/0104 Center 351	11 randomized
Prof. M. Masiak Medical Academy of Lublin, Psychiatry Clinic, ul. Abramowicka 2, 22-442 Lublin, Poland	5077IL/0104 Center 352	3 randomized

Dr. Andrzej Michorzewski Regional Hospital in Lipno, Department of Psychiatry, Lipno, Poland	5077IL/0104 Center 353	9 randomized
Dr. Jaroslaw Laczkowski Wojewodzki Osrodek Leczenia Psychiatrycznego im. Hurynowicz, ul. Curie-Sklodowskiej 27/29, 87-100 Torun, Poland	5077IL/0104 Center 355	7 randomized
Dr. med. Zbigniew Wawarzyniak Psychiatric Hospital in Lodz, Aleksandrowska str 159, 91-229 Lodz, Poland	5077IL/0104 Center 356	5 randomized
Dr. Stefan Krzyminski Psychiatric Hospital in Ciborz, 66-212 Ciborz, Poland	5077IL/0104 Center 357	4 randomized
Dr Tzung-Lieh Yeh National Cheng Kung University, College of Medicine, 138, Sheng-Li Road, Tainan, Taiwan	5077IL/0104 Center 371	1 randomized
Dr. Nan-Ying Chiu Changhua Christian Hospital, 135, Nan Siau Street, Changhua, Taiwan 500 R.O.C.	5077IL/0104 Center 372	2 randomized
Dr. Ching-Kuan Wu Chang Gung Memorial Hospital, 123 Ta-Pei Road, Niao-Sung Hsiang, Kaohsiung Country, Taiwan, R.O.C.	5077IL/0104 Center 373	4 randomized
Dr. Yu, Hsieh- Chao 80, Lane 870, Chung-Shan Road, Jen-Te Hsien, Tainan County, Taiwan, R.O.C.	5077IL/0104 Center 374	6 randomized

Assoc. Prof. Dr. Vihra Milanova Alexandrovska Hospital Female Psychatric Clinic 1G.Sofijski str. Sofia 1431 BULGARIA	5077IL/0105 Center 411	13
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Assoc. Prof. Dr. Georgi Koychev Alexandrovska Hospital Male Psychatric Clinic 1G.Sofijski str. Sofia 1431 BULGARIA	5077IL/0105 Center 413	10
Assoc. Prof. Dr. Ognian Tanchev Univ.Hospital Of Neurology and Psychiatry Tzarigradsko shose IV km Sofia 1113 BULGARIA	5077IL/0105 Center 414	4
Dr. Raina Tzvetkova Regional Psychiatry Hospital 86 Ruski Blvd Plovdiv 4000 BULGARIA	5077IL/0105 Center 415	3

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Dr. Temenuzhka Mateva Regional Psychiatry Hospital 20 Tutrakan Blvd Ruse 7003 BULGARIA	5077IL/0105 Center 416	18
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Dr. Liljana Moro Clinic of Psychiatry, Clinical Hospital Centre Rijeka, Cambierieva 17/1 51,000 Rijeka CROATIA	5077IL/0105 Center 422	3
Prof. Venetsanos Mavreas District General University Hospital of Ioannina (PEPAGNI) University Avenueloannina GREECE	5077IL/0105 Center 431	1
Prof. George Kaprinis AHEPA Hospital of Thessaloniki S. Kyriakidi 1 str. 546 36 Thessaloniki GREECE	5077IL/0105 Center 432	1
Asc. Prof. Vassilis Alevizos Aeginitio Hospital Psychiatric Clinic of	5077IL/0105 Center 433	1

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University of Athens72 Vas. Sofias & 1, Aeginitou Str 115 28 Athens GREECE		
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Dr. V Palaniappun Institute of MentalHealth Kilpauk Chennai INDIA	5077IL/0105 Center 444	25
Dr. MK Deshpande Prof. of Psychiatry, Govt Medical College, Aurangabad, 431001 INDIA	5077IL/0105 Center 445	21
Dr. J Nagpal VIMHANS, No 1 Institutional Area Nehrunager New Delhi 110 065 INDIA	5077IL/0105 Center 447	20

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Robert Levin, M.D.,
October 16, 2003

FDA, CDER, ODE1, DNDP, HFD-120

Cc: NDA
T Laughren
P Andreason
R Levin
D Bates

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/s/

Robert Levin
10/23/03 02:46:41 PM
MEDICAL OFFICER

Thomas Laughren
10/24/03 08:43:00 AM
MEDICAL OFFICER
I agree that these supplements are approvable; see memo to file for more detailed comments.--TPL

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

DATE: October 24, 2003

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Seroquel (quetiapine) for the treatment of manic[ ] episodes in bipolar disorder (both monotherapy and adjunctive therapy)

TO: File NDA 20-639/S-016 and S-017
[Note: This overview should be filed with the 12-30-02 original submission of these supplements.]

1.0 BACKGROUND

Seroquel is currently approved and marketed for the acute treatment of schizophrenia, in an immediate release tablet (NDA 20-639; approved 9-26-97). These supplements provide data in support of a new claim for this same formulation both as monotherapy and as adjunctive therapy for the short-term treatment of manic[ ] episodes in bipolar disorder, in a dose range of 400 to 800 mg/day.

It should be noted that, at the current time, there are 3 drugs specifically approved for the treatment of acute mania, i.e., lithium, Depakote (valproate), and Zyprexa (both monotherapy and adjunctive therapy). While Depakote and Zyprexa are approved only for short-term use in treating mania, lithium is approved for both acute treatment and for maintenance treatment of mania. A fourth drug, Lamictal, has also been approved for maintenance treatment in bipolar disorder, but not for acute treatment.

We had several communications with the sponsor regarding the development program for Seroquel in the short-term treatment of mania:

-In a 5-4-99 letter, we indicated that there was some uncertainty at that time whether or not we would accept only short-term data in support of a mania claim, given that delay of relapse is likely the more important benefit of drug treatment for bipolar disorder. Nevertheless, we noted that, regarding what is needed to support a short-term claim, 1 positive monotherapy trial and 1 positive add-on trial would be enough to support claims for both monotherapy and adjunctive therapy.

-In a 10-13-99 letter, we confirmed that 1 positive monotherapy trial and 1 positive add-on trial would be enough to support claims for both monotherapy and adjunctive therapy.

-In a 9-8-00 letter, we commented positively on their proposal to rely on a distribution of underlying mood stabilizers (i.e., either lithium or valproate) in their adjunctive therapy studies that was consistent with the common practice in the regions where the studies were being conducted. We also commented on the requirements to obtain claims for secondary outcomes.

-In a 5-17-01 meeting that was essentially an end-of-phase 2 meeting, we commented on several key issues:
-It was noted that only 1 of 4 planned studies was to be done in the US; we indicated that the supplement would be problematic if that study was not positive.
-The sponsor indicated that they did not plan to conduct a valproate interaction study, however, representatives from OCPB strongly encouraged them to do this, and provided several arguments why this would be important.
-In response to their question, we again commented on the requirements to obtain claims for secondary outcomes.
-The sponsor made an argument for why they should not be expected to conduct a pediatric bipolar study, and asked for a full waiver. We argued that we were routinely asking for such studies, and our experts advised that they could and should be done.

-On 3-20-02, we held a preNDA meeting with the sponsor, and indicated that, on face, the program should be adequate for filing. The meeting focused mostly on format issues.

Since the proposal is to use the currently approved Seroquel formulation for this expanded population, there was no need for chemistry (except for review of EA data) or pharmacology reviews of this supplement. Drug interaction data from a valproate interaction study were submitted as part of this supplement, and were reviewed by Kofi Kumi, Ph.D. from the biopharmaceutics group. The primary review of the clinical efficacy and safety data was done by Robert Levin, M.D. from the clinical group. Kooros Mahjoob, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The original supplements for this expanded indication were submitted 12-30-03, and the supplement was filed 2-11-03. There was no safety update.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

As Seroquel is a marketed product, there were no chemistry issues requiring review for this supplement, other than for a review of EA data, and this was found to be acceptable.

3.0 PHARMACOLOGY

As Seroquel is a marketed product, there were no pharmacology/toxicology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

Only one drug interaction study was conducted as part of this development program, i.e., a study involving the interaction of quetiapine and valproate. The results of this study were reviewed by Kofi Kumi, Ph.D., from OCPB. This study revealed no effect of valproate on the AUC of quetiapine, however, the Cmax was increased by 17%, and the 90% CI was not contained in the 80-125% limits. Neither rate nor extent of valproate absorption were significantly affected by quetiapine administration. We are in agreement that the slight increase in quetiapine Cmax is of doubtful clinical significance, and OCPB has suggested only minor changes to the sponsor's proposed language describing the results of the valproate study.

A lithium interaction study had been done previously, and showed no effect of quetiapine on the pharmacokinetics of lithium. This finding is already described in labeling.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review focused on results from 4 trials submitted in support of this supplement, i.e., 2 monotherapy trials (IL/0104 and IL/0105) and 2 adjunctive therapy trials (IL/0099 and IL/0100). While these trials were of different durations (see later), for all 4, the primary analyses were at 3 weeks; thus, I will consider these 3-week studies and focus only on the 3-week results. All were multicenter, randomized, double-blind, placebo-controlled, flexible dose studies involving adult ($\geq$18) bipolar I patients (DSM-IV) having manic episodes, with or without psychotic features (Note: study 100 was the exception, in that, it permitted mixed episodes as well). For both the monotherapy and the add-on trials, patients must have been inpatients at the time of entry. In each trial, the primary endpoint was change from baseline to final visit (LOCF) at the end of week 3 for the Young Mania Rating Scale (YMRS) total score, an 11-item scale including items related to both manic and psychotic behavior. I will not comment here on secondary endpoints. The primary analysis was

LOCF using ANCOVA on a modified ITT dataset, i.e., all randomized patients who received at least 1 dose of assigned treatment and who had baseline and at least 1 followup assessment. The statistical model included treatment group and investigator, and the baseline YMRS value as a covariate. Dr. Mahjoob also did analyses using a mixed-effects model, repeated measures approach (MMRM) to check the results; this is a model that uses all available YMRS measures.

5.1.2 Summary of Individual Studies

5.1.2.1 Summary of IL/0104

This study was conducted at 49 sites [all foreign, i.e., the Far East (China, Indonesia, The Phillipines, and Taiwan), South America (Argentina and Chile), and Eastern Europe (Croatia, Estonia, Latvia, Lithuania, and Poland)], and was limited to adult bipolar I inpatients (DSM-IV) having manic episodes (i.e., none with mixed episodes were included). This was a 12-week study, however, as noted, the primary analysis was at 3 weeks, and I will limit my comments to the 3-week data. There was a limited washout of prior psychotropic medications, followed by treatment with either quetiapine, haloperidol, or placebo. Dosing for all treatments was on a bid basis. Quetiapine dosing was initiated with 100 mg on day 1, with daily increases of 100 mg/day, until reaching 400 mg/day on day 4. On day 5, the dose could be adjusted between 200-600 mg/day, and then between 200-800 mg/day for days 6 to 84 (based on efficacy and/or tolerability). Haloperidol was initiated at 2 mg/day, and could be adjusted between 2-8 mg/day on days 6-84.

Patients were slightly more female than male (about 63:37), about 3/4 Caucasian, and the mean age was about 41. The mean quetiapine dose in 3 week completers was 559 mg/day. About ½ of drug-treated patients and about 2/3 of placebo-treated patients received concomitant lorazepam for the management of acute agitation during days 1-14; actual dosing data was not provided.

The intent-to-treat population was as follows:

-Quetiapine 101
-Haloperidol 98
-Placebo 100

Proportions completing to 3 weeks were as follows:
-Quetiapine 80/101 (79%)
-Haloperidol 86/98 (88%)
-Placebo 73/100 (73%)

The results on the primary efficacy analysis are as follows:

Efficacy Results on YMRS Total Score for Study IL/0104 (LOCF)

	Baseline YMRS	Δbaseline YMRS	[P-value(vs pbo)]
Quetiapine (n=101)	**34**	**-12**	**<0.0001**
Haloperidol (n=98)	**32**	**-16**	**<0.0001**
Placebo (n=100)	**33**	**-8**	

While not described here, results on MMRM analysis also favored quetiapine over placebo.

Conclusion: Dr. Levin considered this a positive study, as did Dr. Mahjoob; I agree.

5.1.2.2 Summary of IL/0105

This study was conducted at 38 sites [all foreign, Europe (Bulgaria, Croatia, Greece, Romania, Russia, and Turkey), India, and China], and was limited to adult bipolar I inpatients (DSM-IV) having manic episodes. This was a 12-week study, however, as noted, the primary analysis was at 3 weeks, and I will limit my comments to the 3-week data. There was a brief washout of prior psychotropic medications, followed by treatment with either quetiapine, lithium, or placebo. Dosing of all treatments was on a bid basis. Quetiapine dosing was initiated with 100 mg on day 1, with daily increases of 100 mg/day, until reaching 400 mg/day on day 4. On day 5, the dose could be adjusted between 200-600 mg/day, and then between 200-800 mg/day for days 6 to 84 (based on efficacy and/or tolerability). Lithium was initiated at 900 mg/day, and could be adjusted at the discretion of the investigator on days 5-84.

Patients were slightly more male than female (about 58:42), about 50% Asian and 50% Caucasian, and the mean age was about 40. The mean quetiapine dose in 3 week completers was 586mg/day. About ½ of drug-treated patients and about 2/3 of placebo-treated patients received concomitant lorazepam for the management of acute agitation during days 1-14; actual dosing data was not provided.

The intent population was as follows:
-Quetiapine 107
-Lithium 98
-Placebo 95

Proportions completing to 3 weeks were as follows:
-Quetiapine 102/107 (95%)
-Lithium 88/98 (90%)
-Placebo 79/95 (83%)

The results on the primary efficacy analysis are as follows:

Efficacy Results on YMRS Total Score for Study IL/0105 (LOCF)

	Baseline YMRS	Δbaseline YMRS	[P-value(vs pbo)]
Quetiapine (n=107)	33	-15	**<0.0001**
Lithium (n=98)	33	-15	**<0.0001**
Placebo (n=95)	34	-7	

While not described here, results on MMRM analysis also favored quetiapine over placebo.

Conclusion: Dr. Levin considered this a positive study, as did Dr. Mahjoob; I agree.

5.1.2.3 Summary of IL/0099

This study was conducted at 32 US sites, and was limited to adult bipolar I inpatients (DSM-IV) having manic episodes. All patients were either (1) being maintained on valproate (50 to 100 µg/mL) or lithium (0.7 to 1.0 mEq/L), and experienced the manic episodes despite such maintenance therapy, or (2) were first started on either of these drugs on an open basis prior to randomization (and presumably were not adequately controlled on monotherapy alone). Patients were continued on whatever mood stabilizer they had been on at the time of randomization, with the goal, at least, of keeping them in the same plasma level ranges as indicated above. In fact, exposures achieved were on the low side: the lithium range was 0.74 to 0.80 mEq/L, and the valproate range was 68 to 75 µg/mL. It turned out that valproate was the mood stabilizer utilized in roughly 60% of patients. There was a limited washout of prior psychotropic medications (of course, other than lithuim or valproate), followed by treatment with either quetiapine or placebo. Both treatments were administered on a bid basis, as add-on therapy. Quetiapine dosing was initiated with 100 mg on day 1, with daily increases of 100 mg/day, until reaching 400 mg/day on day 4. On day 5, the dose could be adjusted between 200-600 mg/day, and then between 200-800 mg/day for days 6 to 21 (based on efficacy and/or tolerability).

Patients were roughly 57:43 male to female, the mean age was about 41, and patients were roughly 70% Caucasian. The mean quetiapine dose in 3 week completers was 584mg/day. About ½ of drug-treated patients and about 2/3 of placebo-treated patients received concomitant lorazepam for the management of acute agitation during days 1-14; actual dosing data was not provided.

The intent population was as follows:
-Quetiapine 81
-Placebo 89

Proportions completing to 3 weeks were as follows:
-Quetiapine 53/81 (65%)
-Placebo 47/89 (53%)

The ANCOVA model was as described above. The results on the primary efficacy analysis are as follows:

Efficacy Results on YMRS Total Score for Study IL/0099 (LOCF)

	Baseline YMRS	Δbaseline YMRS	[P-value(vs pbo)]
Quetiapine (n=81)	32	-14	**0.021**
Placebo (n=89)	31	-10	

While not described here, results on MMRM analysis also favored quetiapine over placebo.

Conclusion: Dr. Levin considered this a positive study, as did Dr. Mahjoob; I agree.

5.1.2 Summary of IL/0100

This study was conducted at 44 foreign sites [Canada, Europe, India, and South Africa], and included bipolar I inpatients (DSM-IV) having manic or mixed episodes. While this was a 42-day study, I will focus on the 3 week results, since the primary analysis was at 21 days. All patients were either (1) being maintained on valproate (50 to 125 μg/mL) or lithium (0.6 to 1.4 mEq/L), and experienced the manic or mixed episodes despite such maintenance therapy, or (2) were first started on one of these 2 drugs on an open basis prior to randomization (and presumably were not adequately controlled on monotherapy alone). Patients were continued on whatever mood stabilizer they had been on at the time of randomization, with the goal, at least, of keeping them in the same plasma level ranges as indicated above. In fact, exposures achieved were on the low side: the lithium range was 0.74 to 0.80 mEq/L, and the valproate range was 68 to 75 μg/mL. It turned out that lithium was the mood stabilizer for 83% of patients, with the remaining 17% receiving valproate. Quetiapine dosing was initiated with 100 mg on day 1, with daily increases of 100 mg/day, until reaching 400 mg/day on day 4. On day 5, the dose could be adjusted between 200-600 mg/day, and then between 200-800 mg/day for days 6 to 42 (based on efficacy and/or tolerability).

Patients were approximately 50:50 male to female, the mean age was about 40, and patients were about 74% Caucasian. The mean quetiapine dose in 3 week completers was 423 mg/day. About ½ of drug-treated patients and about 2/3 of placebo-treated patients received concomitant lorazepam for the management of acute agitation during days 1-14; actual dosing data was not provided.

The intent population was as follows:
-Quetiapine 104
-Placebo 96

Proportions completing to 3 weeks were as follows:
-Quetiapine 92/104 (88%)
-Placebo 78/96 (81%)

The ANCOVA model was as described above. The results on the primary efficacy analysis are as follows:

Efficacy Results on YMRS Total Score for Study IL/0100 (LOCF)

	Baseline YMRS	Δbaseline YMRS	[P-value(vs pbo)]
Quetiapine (n=104)	32	-15	**0.281**
Placebo (n=96)	33	-13	

Conclusion: The MMRM analysis was also negative, and there was general agreement that this was a negative study.

5.1.3 Comment on Other Important Clinical Issues Regarding Efficacy

Evidence Bearing on the Question of Dose/Response for Efficacy

There was no evidence provided in this application pertinent to the question of dose response for effectiveness.

Clinical Predictors of Response

Exploratory analyses were done, when feasible, to detect subgroup interactions on the basis of gender, age, and race. There was no clear indication of differences in response based on these variables, however, there was likely not adequate power to detect such differences.

Size of Treatment Effect

The effect size as measured by difference between drug and placebo in change from baseline in the YMRS total score observed in the positive studies was similar to that seen in other positive mania trials, and I consider this a sufficient effect to support an efficacy claim for this product in mania, both monotherapy and as adjunctive therapy.

Duration of Treatment

While the data from secondary analyses of these studies, particularly the 12 week data for the monotherapy studies, were suggestive of benefits beyond 3 weeks, we cannot draw any conclusions about these results, given that they were secondary analyses. Thus, no definitive data were presented in this supplement pertinent to the question of the longer-term efficacy of quetiapine in mania.

5.1.4 Conclusions Regarding Efficacy Data

These 3 positive trials (2 for monotherapy and 1 for adjunctive therapy) support the claim for short-term efficacy of quetiapine, either as monotherapy or as adjunctive therapy, in the treatment of bipolar I patients with emergent manic[ ] episodes (either in drug free patients or in patients on maintenance treatment with either valproate or lithium). The question of longer-term efficacy will have to be addressed in the future, as will the question of use in pediatric bipolar disorder.

5.2 Safety Data

Clinical Data Sources for Safety Review

The safety data in the original submission for quetiapine in the treatment of mania were derived primarily from a total of n=208 quetiapine-exposed patients in monotherapy studies and n=196 quetiapine-exposed patients in add-on studies, representing a total person-time of about 49 years. These were 21-day studies (for the primary efficacy endpoint), with longer-term, placebo-controlled extensions. As noted, the quetiapine doses ranged from 400-800 mg/day. The safety review also examined data submitted as part of a PSUR submitted with the original supplements. As noted, there was not a formal literature review, however, some general references were provided.

Overview of Safety Findings

Safety Profile in Clinical Trials:

Overall, the profile of adverse events, labs, vital sign, and ECGs observed in this relatively small sample of patients was not obviously different from that seen in the original NDA population, and there were no new, unrecognized serious adverse events that could be reasonably considered related to quetiapine use. There were 3 deaths, including 2 in the placebo groups and 1 in a quetiapine patient that was not reasonably attributable to quetiapine. There were a total of 17 SAEs among quetiapine-exposed patients, compared to 25 among placebo patients. Only 2 of the SAEs in quetiapine-exposed patients could be reasonably attributed to this drug (syncope and orthostatic hypotension). All of the quetiapine dropouts for likely drug-related adverse events were for events known to be associated with this drug. The following expected changes were seen with quetiapine: slight weight gain; modest decrease in thyroxine, but no patients with clinical hypothyroidism. Of note, there were 2 quetiapine-exposed patients with neutropenia. There was no difference from placebo in mean change from baseline in glucose. No ECG effect was demonstrated. The profile of common and drug-related adverse events emerging from this database was as follows: somnolence, asthenia, dizziness, dry mouth, weight gain, and orthostatic hypotension.

PSUR:

The PSUR covered a period from 8-1-01 to 7-31-02, and included both spontaneous reports as well as some limited data from several clinical trials in populations other than bipolar. I will focus my comments on new information derived from spontaneous reports. These reports revealed new findings in two areas. First, there were reports of additional overdose cases, included fatal cases, as well as cases involving other serious consequences, e.g., coma, seizures, various serious cardiac events[ ] [ ] In addition, there are reports of serious events that are uncommon as background events and are not listed in currently approved labeling, including, but not limited to, the following: rhabdomyolysis, anaphylaxis, hyponatremia/SIADH, SJS. There are additional reports of neutropenia. We will ask the sponsor to modifiy both the Overdose section and the Postmarketing Reports sections of Seroquel labeling, with new language to address these new findings.

Future Needs:

While quetiapine has been demonstrated to be reasonably safe in this population, either as monotherapy or as add-on therapy, there is a need for longer-term safety data in this population, given the likelihood that it will be used more chronically. Of particular interest would be the issue of induction of either mania or depression during longer-term use. There are literature reports suggesting the possibility of mania induction with this drug, despite the demonstrated advantages for mania during shorter-term use.

5.3 Clinical Sections of Labeling

We have made relatively minor changes to the sponsor's proposed additions to labeling based on this supplement.

6.0 WORLD LITERATURE

While no formal literature review was provided in these supplements, the sponsor did provide several general references, which were reviewed by Dr. Levin. He did not discover any previously unrecognized important safety concerns for this drug. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, quetiapine is not approved for the treatment of mania, either as monotherapy or as adjunctive therapy, in any countries. We will ask for a regulatory status update in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 2 foreign sites for supplement 16: Satkeviciute (Lithiuania) and Andrezina (Latvia), both from study 104. The Satkeviciute site was classified as NAI and the Andrezina site was classified as VAI, based on minor deficiencies. Overall, the data from these 2 sites were judged to be acceptable.

Inspections were conducted at 2 US sites for supplement 17: Bari (Chula Vista, CA) and Goenjian (Long Beach, CA), both from study 99, the sole positive add-on study. Both sites were classified as VAI, based on minor deficiencies. Overall, the data from these 2 sites were judged to be acceptable.

10.0 APPROVABLE LETTER

An approvable letter acknowledging our decision to proceed with an approval action pending agreement on labeling has been included with the approvable package. We have also asked for a safety update, a regulatory status update, and an updated literature review.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that AstraZeneca has now submitted sufficient data to support the conclusion that Seroquel is effective and acceptably safe for both monotherapy and as adjunctive therapy in the acute treatment of mania. I recommend that we issue the attached approvable letter with our proposed labeling for this product.

cc:
Orig NDA 20-639/S-016 & 017 (Seroquel/Mania)
HFD-120/Division File
HFD-120/TLaughren/RKatz/RLevin/DBates

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/s/

Thomas Laughren
10/24/03 08:00:42 AM
MEDICAL OFFICER

FOOD and DRUG ADMINISTRATION

CENTER for DRUG EVALUATION and RESEARCH

DIVISION of NEUROPHARMACOLOGICAL DRUG PRODUCTS

(HFD-120)

Brand Name:	SEROQUEL ®
Generic Name:	Quetiapine [redacted]
Drug Category:	Antipsychotic
Sponsor:	AstraZeneca
Indication:	Acute Mania of Bipolar Disorder
NDA Numbers:	20-639/S-016 and S-017
Correspondence Date:	November 12, 2003
Medical Reviewer:	Robert Levin, M.D.

Type of Review: Analysis of Sponsor's Response to Division's Approvable Letter

I. Background

On October 27, 2003, the Division sent the sponsor an approvable letter regarding supplemental NDAs 20-639/S-016 and 20-639/S-017 (acute treatment of mania with quetiapine as monotherapy or adjunctive therapy). On November 12, 2003, the sponsor submitted a response that addresses the requests of the Division. The main items include changes in labeling of several sections, a safety update, a World Literature Update, and a Post Marketing Update.

II. Sources of Information

A. "Response to the approvable letter from the FDA (dated 27 October 2003) regarding the supplemental new drug application S-016 and S-017 for SEROQUEL® (quetiapine fumarate) tablets – Safety Update"

B. **"Post Marketing Update for Bipolar Mania Submission Seroquel (November 7, 2003)"**

III. Estimated Cumulative Seroquel Exposure

It is estimated that about 6.1 million patients worldwide (an estimate of almost 5.2 million patients in the US and 0.9 million patients ex-US) have been exposed to quetiapine for all time through 30 September 2003 for the US, and through 31 March 2003 for ex-US. Patient years of quetiapine use were calculated from the number of

tablets delivered to wholesalers worldwide since SEROQUEL was first launched in 1997 (international birth date). A daily dose of 300 to 450 mg/patient/day was assumed, based upon 1-year exposure. It is estimated that there have been 1,443,083 to 2,164,625 patient years of quetiapine use since the international birth date, based on the assumed average daily dose.

IV. Labeling Changes

The sponsor has proposed a number of revisions. The Division accepts several of the minor amendments; however, the Division would like to retain most of the labeling language that was sent to the sponsor along with the approvable letter. The sponsor would like to make references to "12-week trials," including the 9-week extensions of the pivotal, acute, 3-week, monotherapy trials. Since the sponsor did not prospectively designate the 12-week time points as primary or secondary endpoints, the sponsor could not make a claim for the trials for a time frame beyond 3 weeks, which was clearly the primary endpoint agreed upon prospectively by the Division and the sponsor. The indication sought is acute mania in patients with Bipolar Disorder, where the acute period was prospectively defined as 3 weeks. Relevant sections include **Clinical Efficacy Data*/Bipolar Mania***, the description of clinical trial results in the monotherapy and adjunctive therapy trials, **INDICATIONS AND USAGE, Bipolar Mania** section.

The Division has made substantial changes in the OVERDOSE section. Labeling must include the fact that overdose with SEROQUEL, alone or in combination with other medications, has been associated with death. Overdose with SEROQUEL has also been associated with coma, seizure, [ ] hypotension, prolongation of the QT interval, and other serious cardiac events.

V. Safety Update for Clinical Trials

A. Clinical Studies [ ] and US/0043

The safety update presents the adverse events from [ ] recent clinical studies of quetiapine in indications other than bipolar mania. [ ] [ ] [ ]. The second of these studies (5077US/0043), in patients with schizophrenia, had database lock on 18 November 2002; although database lock occurred approximately 6 weeks before the submission date, the sponsor states that data from this study represent a substantial contribution to the safety profile of quetiapine and are therefore included in this update.

Study number	Study title	Date of database lock
[ ]		[ ]
5077US/0043	A Multicenter, Double-blind, Randomized Comparison of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) and Risperidone (RISPERDAL™) in the Treatment of Patients with Schizophrenia	18 November 2002

No new or unexpected safety findings were reported in the[ ]recent clinical trials. The patterns of adverse events reported in the studies are similar to those seen in the previous quetiapine clinical trials. [ ]
[ ]
[ ] In study US/0043, the most commonly reported adverse events were somnolence, headache, weight gain, dizziness, dry mouth, and dyspepsia. The sponsor did not provide information about deaths, serious adverse events, or discontinuations due to adverse events for these[ ]trials.

VI. Worldwide Literature Update

The sponsor conducted a search of the medical literature for the period 1 August 2003 to 6 November 2003, in order to identify any articles pertaining to the safety of quetiapine published since the most recent PSUR, submitted to the FDA on 25 September 2003, was produced. The search was conducted by Leonard A. Jankauskas MS, Product Literature Content Manager and Research Information Scientist, AstraZeneca using the AstraZeneca database "Product Literature at the net" (PL@net). (See Appendix C for a summary of Mr. Jankauskas' credentials). The PL@net database includes publications that are cited in MEDLINE® and other databases. A query was conducted on the English-language database using the controlled vocabulary term "quetiapine"; the results were subsequently queried for entries pertinent to "adverse events", "toxicity", and "poisonings." Publications that included only single case reports or reviews of the primary literature were not included. Results of the query were reviewed for pertinence to drug safety and were categorized by the topics used in the most recent PSUR. The results of the search are listed in Appendix B. The abstracts presented are either those generated by Thomson ISI® (producers of Current Contents), based on a review of the entire article, or are the original published abstracts. The literature items identified via the search were reviewed by Jamie Mullen MD, Senior Director, Clinical Research, AstraZeneca. Based on this medical review, the sponsor believes that the results of the literature search are consistent with the conclusions articulated in the PSUR submitted 25 September 2003 and that no new concerns pertaining to the safety of quetiapine have been identified.

I reviewed the 33 journal article abstracts provided by the sponsor. Twenty-one of these pertained to glucose metabolism or diabetes mellitus. Others pertained to hyperlipidemia, prolactin, use in pregnancy, QT prolongation, overdose, and pediatric use of quetiapine. There were no new or unexpected findings that would change the safety profile of quetiapine treatment.

VII. Post Marketing Update for Bipolar Mania Submission (Seroquel) 11-7-03

A. **Adverse Events Reported in the Post Marketing Period**

The AstraZeneca safety database (Clintrace) contains global AE reports, from consumers, health care professionals, registries, clinical trials, and literature articles for SEROQUEL. For clinical studies, only reports that have a serious AE associated with them are stored in Clintrace. The following summary is based on information in Clintrace through 28 October 2003.

There are no new or unexpected safety findings, based on post-marketing reports. The information is nearly identical to the safety information submitted in the PSUR covering August 1, 2001 to July 31, 2002. That PSUR has been reviewed in detail as part of the sNDA review. As in the PSUR, several types of serious adverse events are discussed: Stevens Johnson Syndrome, Anaphylactic Reactions, Rhabdomyolysis, Elevated Blood Creatine Phosphokinase Concentration, Hyponatremia and SIADH, Agranulocytosis, and Neutropenia. All of these adverse events were identified during the integrated review of safety and the review of the PSUR which had been submitted originally with the sNDA submission.

B. Regulatory Update
The status of all actions taken or pending by Health Authorities with regard to SEROQUEL for the time period of 1 August 2002 through 27 October 2003 have been provided by the sponsor in this submission.

There have been no withdrawals or suspensions, restrictions on distributions, changes in target populations or indications or formulation changes taken for safety reasons during this PSUR period.

Conclusions and Recommendation
In summary, the sponsor has provided a detailed and adequate response to the Division's approvable letter. The findings from the safety updates and literature updates have not revealed any new or unexpected safety findings.

Many of the sponsor's proposed changes in labeling would not be acceptable, since they are not consistent with the indication sought or the endpoints that the Division and the sponsor had agreed upon.

I recommend that the Division discuss the labeling items, before taking an approval action for this supplemental NDA.

Robert Levin, M.D., December 2, 2003
Medical Reviewer,
FDA CDER ODE1 DNDP HFD 120

cc: HFD 120

T Laughren
P Andreason
D Bates

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/s/

Robert Levin
12/2/03 03:03:29 PM
MEDICAL OFFICER

Thomas Laughren
1/8/04 02:16:38 PM
MEDICAL OFFICER
We have reached agreement on final labeling, and I agree that these supplements can now be approved.--TPL

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

DATE: January 8, 2004

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Seroquel (quetiapine) for the treatment of manic[ ] episodes in bipolar disorder (both monotherapy and adjunctive therapy)

TO: File NDA 20-639/S-016 and S-017
[**Note:** This overview should be filed with the 11-11-03 response to our 10-27-03 approvable letter.]

The sponsor responded to our 10-27-03 approvable letter with an 11-11-03 complete response, including a safety update, a world literature update, a postmarketing update, and a counter-proposal for labeling. These materials were reviewed by Robert Levin, M.D., from the clinical group.

The safety update included data from 2 clinical trials, one in dementia and one in schizophrenia. Dr. Levin concluded that no new or unexpected safety findings were revealed in these studies.

The literature update included abstracts for 33 published papers, and these were reviewed by Dr. Levin. Again, he concluded that there were no new or unexpected safety findings.

The postmarketing update included information through 10-28-03, and was almost identical to the PSUR reviewed as part of a previously submitted update to the original submission. Thus, he again concluded that there were no new or unexpected safety findings revealed in this update.

Negotiations over final labeling occurred over a roughly 1 month period, and we reached final agreement as of 1-8-04. Importantly, we have not included a reference in labeling to the monotherapy trials as 12-week studies, since this had not been adequately documented as a key secondary analysis. However, the sponsor has indicated that they do have internal documentation for such specification, and they will plan to submit this in support of a labeling supplement, postapproval, to gain this additional language in labeling. We have agreed to most of the sponsor's other modest changes to labeling.

Conclusions and Recommendations: I believe that AstraZeneca has now submitted sufficient data to support the conclusion that Seroquel is effective and acceptably safe for both monotherapy and as adjunctive therapy in the acute treatment of mania. I recommend that we issue the attached approval letter with our mutually agreed upon final labeling.

cc:
Orig NDA 20-639/S-016 & 017 (Seroquel/Mania)
HFD-120/Division File
HFD-120/TLaughren/RKatz/RLevin/DBates/RNighswander

DOC: MEMSRQMN.AP1

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/s/

Thomas Laughren
1/8/04 02:22:15 PM
MEDICAL OFFICER

Review of NDA Labeling Supplement

Sponsor:	AstraZeneca
NDA:	20-639/SE16; SE17
Brand Name:	SEROQUEL ®
Generic Name:	Quetiapine [ ]
Drug Category:	Antipsychotic
Indication:	Mania of Bipolar Disorder
Correspondence Date:	January 22, 2004 & Aril 13, 2004
Information Submitted:	Documentation of Statistical Analysis Plan and Unblinding Procedures
Medical Reviewer:	Robert Levin, M.D.

I. Background

The sponsor has submitted a labeling supplement for the indication of Mania associated with Bipolar Disorder, in order to describe in labeling the positive results of a proposed secondary outcome measure: the change in mean Young Mania Rating Scale score (YMRS) at the end of 12 weeks of quetiapine monotherapy in two trials. The sponsor had previously submitted supplemental NDAs 20-639 SE16 and SE17 for the indication of acute (3 weeks) treatment of mania. The supplemental NDA was approved, based on the efficacy and safety results from two acute monotherapy trials of quetiapine in subjects with mania associated with Bipolar Disorder (studies IL/0104 and Il/0105). Although the sponsor simultaneously submitted efficacy and safety data for the full 12 weeks of the trials and mentioned in proposed labeling the "12-weeks [ ]" of the studies, it initially appeared that the sponsor had not prospectively designated the 12-week endpoint as a key secondary efficacy endpoint in the statistical analysis plans. In the Statistical Analysis Plan originally submitted (dated June 30, 2000), the secondary endpoint (the change in mean YMRS score at 12 weeks) was not designated as a key secondary endpoint. The statistical analysis plan specified that "the change from baseline in YMRS score at week 12 (LOCF)" would be analyzed as part of an "exploratory analysis." The single protocol amendment (dated July 27, 2000) submitted to the Division did not contain a statistical analysis plan designating the 12-week endpoint as a key secondary endpoint. However, the sponsor stated that a subsequent amendment did contain an SAP that designated the 12-week endpoint as a key secondary outcome measure.

On January 6, 2004, the Division held a teleconference with the sponsor during which the sponsor requested that the Division formally consider approving a labeling supplement to include a description in labeling of the efficacy results at the proposed 12-week secondary endpoint. The Division stated that we would consider the request, if the sponsor would submit documentation of the prospective statistical analysis plans that specified the plan to analyze the 12-week endpoints as key secondary efficacy measures in studies IL/0104 and IL/0105.

II. Review of the Labeling Supplement Documents

A. Contents of the Submission

The sponsor has submitted: 1) "Documentation of Statistical Analysis Lock Dates and Data Unblinding Dates for the Quetiapine Mania Studies"; 2) A hardcopy of the Statistical Analysis Plan (dated August 21, 2002) for the two relevant studies (**0104** and **0105**).

B. Review of the Statistical Analysis Plan Amendment and Supporting Documention

The sponsor states that prior to unblinding of studies 104 and 105, the Statistical Analysis Plan had defined the 12-week assessment of YMRS scores as an outcome measure. "Within each SAP, the 12-week YMRS endpoint was defined prospectively as the pre-eminent secondary endpoint." In addition, it was specified that this secondary endpoint would be analyzed only if the primary endpoint was positive. The sponsor also states that supportive documentation includes the validated dates for the finalization and lock of the SAP, unblinding dates, and other supportive information.

Sponsor's Table of Document Lock and Unblinding Dates

Document Title	Document Lock Date (GEL Version Created)	Database Unblinding Date (DIPLOMAT)
Statistical Analysis Plan for Study 5077IL/0105	August 26, 2002	August 28, 2002
Statistical Analysis Plan for Study 5077IL/0105	September 5, 2002	September 18, 2002
Statistical Analysis Plan for combined studies 5077IL/0104 and 5077IL/0105	August 22, 2002	N/A

In the newly received Statistical Analysis Plan amendment, the change from baseline in mean YMRS score at Day 84 is listed first among the 14 secondary outcome measures. In the SAP section regarding multiplicity analysis, the sponsor states: "The considerations made for addressing multiplicity in Trial 104 and Trial 105 are fully documented in the corresponding study SAP. The primary analysis in both trials is a two-group comparison of a single null hypothesis, i.e. change from baseline in YMRS total score at Day 21 (LOCF) in quetiapine versus placebo, tested at a significance level of 0.05. Successful outcomes of the primary analysis in both these trials are regarded as substantial evidence that quetiapine is more effective than placebo in the treatment of acute mania. If and only if the primary analysis is statistically significant, an analogous confirmatory analysis of the change from baseline in YMRS at Day 84 (LOCF) will be made to evaluate the maintenance of effect. This stepwise sequential procedure will be used within Trial 104, Trial 105 and for the integrated analyses across Trial 104 and Trial 105 in order to ensure a multiple level of significance of 0.05. The multiple level of significance is controlled for given that no confirmative claim is made for maintenance of effect unless the primary analysis is significant. This is in accordance with the CPMP guideline, points to consider on multiplicity issues in clinical trials."

Global Electronic Library Time-Stamp System

significantly superior to placebo (P0.0001). There was no statistically significant difference between quetiapine and haloperidol treatments.

The results of Study 105 are similar, except for the comparison of quetiapine with lithium at Day 84. Treatment with quetiapine was superior to treatment with placebo, and treatment with lithium was superior to treatment with placebo.

Table 2. ***(Monotherapy Study IL/0105):*** Reviewer's Efficacy Analysis Results of Change in Mean YMRS Scores (LOCF)

Day of Assessment	Attribute	Study IL/0105					
		Treatment			Comparison		
		QTP	PLA	LIT	QTP - PLA	LIT - PLA	QTP – LIT
Day 21	N (MITT)	107	95	98	--	--	--
	Mean Δ	-16.07	-8.61	-17.29	-7.56	-9.00	1.44
	P-Val	--	--	--	**<0.0001**	**<0.0001**	0.3979
Day 84	N (MITT)	107	95	98	--	--	--
	Mean Δ	-17.37	-12.90	-18.78	-4.31	-5.91	1.59
	P-Val	--	--	--	**0.0043**	**0.0002**	0.2344

At Day 21, quetiapine treatment was statistically significantly superior to placebo treatment ($P < 0.0001$), and lithium treatment was statistically significantly superior to placebo treatment ($P < 0.0001$). There was no statistically significant difference between quetiapine and lithium ($P=0.3979$). At Day 84, quetiapine treatment was statistically significantly superior to treatment with placebo ($P = 0.0043$). Haloperidol treatment was statistically significantly superior to placebo treatment ($P =0.0002$). There was no statistically significant difference between quetiapine treatment and lithium treatment.

IV. Safety Analysis

Results of the 12-week safety data indicate that quetiapine monotherapy in subjects with Bipolar Disorder, Manic Episode was reasonably safe and tolerable. There were no new or unexpected safety concerns with quetiapine treatment in this study population.

V. Conclusions and Recommendations

In my opinion, the sponsor has provided sufficient documentation to support the claim that the 12-week endpoint was prospectively designated as a key secondary outcome measure. The sponsor has submitted a signed Statistical Analysis Plan stamp-dated through the Global Electronic Library System on August 21, 2002, which was before the dates of unblinding of the two 12-week trials. I recommend that the Division take an approvable action for sNDA 20,639/SLR-020.

The sponsor states that the Global Electronic Library (GEL) timestamp system allows the sponsor to verify the date that a document was received in the system. Each document includes a unique Version Identifier and Version Created Date and Timestamp. Whenever a document is modified and approved in GEL, the Version Identifier and the Version Created date and time are updated. Therefore, the system records when a document was last approved and locked from further modification. The sponsor states that these attributes are "system maintained" and cannot be manually altered. After the SAPs were finalized in GEL system, the signature pages were printed for wet ink signatures. When printed, each signature page is watermarked at the bottom of the page with a number of relevant features.

The sponsor has provided documentation that the original statistical analysis plan was entered into the Global Electronic Library on August 22, 2002 at 08:31:48, which was before the dates of unblinding. In addition, the Statistical Analysis Plan contains the handwritten signatures (dated August 22, 2002) of the Project Statistician, the Global Product Statistician, and the Global Project Team Physician.

[ ] Database Unblinding

The sponsor states that with the [ ] system, study randomization schemes are created and stored and that an electronic system log records the identity of any user who broke the randomization, as well as the date of the unblinding. The sponsor states that unblinding for Study 104 occurred on August 28, 2002 and that unblinding of Study 105 occurred on September 18, 2002.

III. Efficacy Results for the 12-Week Quetiapine Monotherapy Studies

Studies 104 and 105 had nearly identical designs. They were multicenter (all non-U.S.), randomized, double-blind, placebo-controlled, flexible-dose, quetiapine monotherapy trials with a 3-week acute phase and a 9-week extension phase. In study 104, there was a haloperidol treatment arm, and in Study 105, there was a lithium treatment arm for the purpose of determining assay sensitivity. Subjects were adult inpatients with a diagnosis of Bipolar I Disorder, Manic Episode. Study 104 included 302 subjects at 50 international sites, and Study 105 included 302 subjects at 38 international sites. The table below illustrates details regarding the studies

Table. Quetiapine as Monotherapy in 12-Week, Placebo-Controlled Trials

TRIAL NUMBER DATES	TRIAL DESIGN & OBJECTIVE	STUDY DRUG REGIMENS	DISPOSITION of SUBJECTS
IL/0104 49 International sites (Europe, Asia, South America) 1-7-01 to 4-25-02	Multicenter, randomized, double-blind, placebo-controlled, parallel group, flexible-dose study to assess the anti-manic efficacy and safety of quetiapine monotherapy in subjects with Bipolar I Disorder, Manic Episode. **Duration** 21 days for primary analysis 84 days of double-blind treatment **Quetiapine Exposure** Days 1-21: 5.1 subject-years Days 1-84: 15.4 subject-years	**Quetiapine:** Flexible-dose: 100-800 mg orally, divided BID **Haloperidol:** Flexible-dose: 2-8 mg orally, divided BID **Placebo:** matching tabs; flexible-BID	Screened: 353 Randomized: 302 (86%) Treated: 299 Quetiapine: 101 Placebo: 100 Haloperidol: 98 **Discontinued [Day 21, Day 84** Discontinued: 33%, 50% Quetiapine: 35%, 46% Placebo: 40%, 58% Haloperidol: 22%, 46%
IL/0105 38 International sites (Europe & Asia) 4-3-01 to 5-27-02	(Lithium arm used for assay sensitivity instead of haloperidol. Otherwise, the study design was identical to that of IL/0104). **Duration** 21 days for primary analysis 84 days of double-blind treatment **Quetiapine Exposure** Days 1-21: 5.9 subject-years Days 1-84: 20.3 subject-years	**Quetiapine:** Flexible-dose: 100-800 mg orally, divided BID **Lithium:** Day 1: 900 mg/day. Target serum Li level: 0.6-1.4 mEq/ L **Placebo:** matching tabs; flexible-doses Orally, divided BID	Screened: 370 Randomized: 302 (82%) Treated: 302 Quetiapine: 107 Placebo: 97 Lithium: 95 **Discontinued [Day 21, Day 84** Discontinued: 18%, 42% Quetiapine: 9%, 33% Placebo: 30%, 64% Lithium: 14%, 32%

Summary of Statistical Reviewer's Efficacy Results for Study 104 & 105

In summary, both studies were positive at both the 3-week and 12-week endpoints. Dr. Mahjoob has constructed summary tables shown below.

Table 1. ***(Monotherapy Study IL/0104):*** Reviewer's Efficacy Analysis Results of the Mean Change in YMRS scores (LOCF)

Day of Assessment	Attribute	Study IL/0104					
		Treatment			Comparison		
		QTP	PLA	HAL	QTP - PLA	HAL - PLA	QTP – HAL
Day 21	N (MITT)	101	100	98	--	--	--
	Mean • •	-13.14	-8.80	-16.37	-4.34	-7.19	2.86
	P-Val	--	--	--	**0.0089**	**<0.0001**	0.0783
Day 84	N (MITT)	101	100	98	--	--	--
	Mean • •	-18.86	-10.62	-20.18	-8.92	-7.61	-1.32
	P-Val	--	--	--	**<0.0001**	**<0.0001**	0.4478

At Day 21, quetiapine was statistically significantly superior to placebo (P=0.0089). Haloperidol was also statistically significantly superior to placebo (P<0.0001); however, there was no statistically significant difference between quetiapine and haloperidol. At Day 84, quetiapine was statistically significantly superior to placebo (P<0.0001), and haloperidol was statistically

significantly superior to placebo (P0.0001). There was no statistically significant difference between quetiapine and haloperidol treatments.

The results of Study 105 are similar, except for the comparison of quetiapine with lithium at Day 84. Treatment with quetiapine was superior to treatment with placebo, and treatment with lithium was superior to treatment with placebo.

Table 2. ***(Monotherapy Study IL/0105):*** Reviewer's Efficacy Analysis Results of Change in Mean YMRS Scores (LOCF)

Day of Assessment	Attribute	Study IL/0105					
		Treatment			Comparison		
		QTP	PLA	LIT	QTP - PLA	LIT - PLA	QTP – LIT
Day 21	N (MITT)	107	95	98	--	--	--
	Mean • •	-16.07	-8.61	-17.29	-7.56	-9.00	1.44
	P-Val	--	--	--	**<0.0001**	**<0.0001**	0.3979
Day 84	N (MITT)	107	95	98	--	--	--
	Mean • •	-17.37	-12.90	-18.78	-4.31	-5.91	1.59
	P-Val	--	--	--	**0.0043**	**0.0002**	0.2344

At Day 21, quetiapine treatment was statistically significantly superior to placebo treatment ($P < 0.0001$), and lithium treatment was statistically significantly superior to placebo treatment ($P < 0.0001$). There was no statistically significant difference between quetiapine and lithium ($P=0.3979$). At Day 84, quetiapine treatment was statistically significantly superior to treatment with placebo ($P = 0.0043$). Haloperidol treatment was statistically significantly superior to placebo treatment ($P =0.0002$). There was no statistically significant difference between quetiapine treatment and lithium treatment.

IV. Safety Analysis

Results of the 12-week safety data indicate that quetiapine monotherapy in subjects with Bipolar Disorder, Manic Episode was reasonably safe and tolerable. There were no new or unexpected safety concerns with quetiapine treatment in this study population.

V. Conclusions and Recommendations

In my opinion, the sponsor has provided sufficient documentation to support the claim that the 12-week endpoint was prospectively designated as a key secondary outcome measure. The sponsor has submitted a signed Statistical Analysis Plan stamp-dated through the Global Electronic Library System on August 21, 2002, which was before the dates of unblinding of the two 12-week trials. I recommend that the Division take an approvable action for sNDA 20,639/SLR-020.

Robert Levin, M.D., May 11, 2004
Medical Reviewer,
DNDP CDER FDA

Cc: HFD 120
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Robert Levin
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Thomas Laughren
5/18/04 08:00:55 AM
MEDICAL OFFICER
I agree that this supplement can now be approved;
see memo to file.--TPL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-639/S-016 & S-017

CHEMISTRY REVIEW(S)

NDA 20-639, SE1-016
NDA 20-639, SE1-017

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-639 **DATE REVIEWED: 6/8/03**

REVIEW #: 1 **REVIEWER:** Donald N. Klein, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	12/30/02	12/30/02	1/2/03

NAME & ADDRESS OF APPLICANT:
AstraZeneca UK Limited
Alderley Park
Macclesfield, Cheshire, SK10 4TG
England

DRUG PRODUCT NAME:
Proprietary: Seroquel®
Established (USAN) (1996): quetiapine fumarate

PHARMACOL. CATEGORY/INDICATION:
S-016: Monotherapy Indication

S-017: Adjunctive Therapy Indication

DOSAGE FORM: film-coated tablet

STRENGTHS: 25 mg, 100 mg, 150 mg, 200 mg, and 300 mg

ROUTE OF ADMINISTRATION: Oral

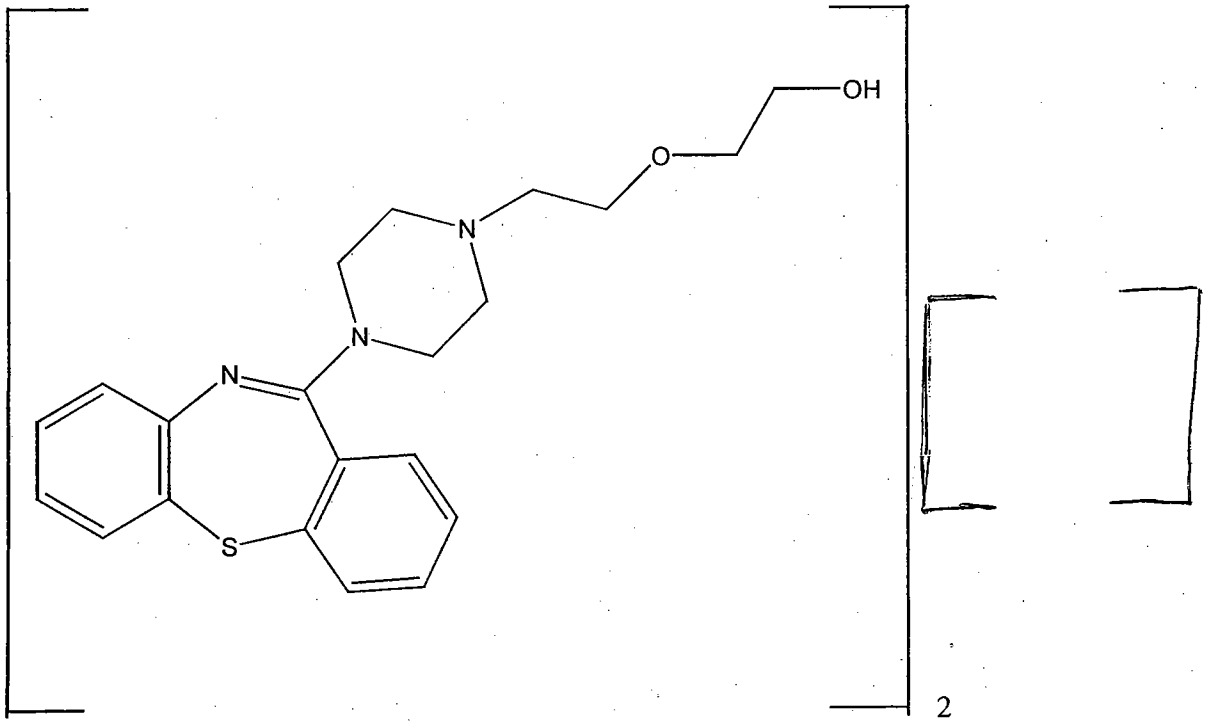
Rx/OTC: *Rx*

SPECIAL PRODUCTS: __Yes xx No

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

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

Molecular formula: $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$
MW: 883.11
CAS: 111974-72-2



EFFICACY SUPPLEMENTS PROVIDE FOR: Treatment of acute bipolar mania: monotherapy indication (S-016) and adjunctive therapy indication (S-017).

SUPPORTIVE APPLICATIONS: DMFs [ ]

CONCLUSIONS: Recommend Approval of the CMC section.

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Chemistry Review

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/s/

Donald Klein
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CHEMIST

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Thomas Oliver
6/9/03 10:00:31 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-639/S-016 & S-017

EA/FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

SEROQUEL® TABLETS
(quetiapine fumarate)

NDA 20-639 / S-016
Treatment of acute bipolar mania (mono-therapy)

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neurological Drug Products
(HFD-120)

January 28, 2003

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-639 / S-016

SEROQUEL® TABLETS (quetiapine fumarate)
Treatment of acute bipolar mania (mono-therapy)

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 has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

This supplement requests approval of Seroquel Tablets (quetiapine fumarate) for treatment of acute polar mania (mono-therapy). In support of its supplemental 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 is a chemically synthesized drug currently approved for treatment of acute and chronic psychoses, including schizophrenia.

Quetiapine fumarate and its metabolites and conjugates may enter the aquatic environment from patient use and disposal. Quetiapine fumarate is not degraded by aerobic and anaerobic, hydrolytic and photolytic mechanisms. 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
Florian Zielinski
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Nancy B. Sager
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Yuan-yuan Chiu, Ph.D.
Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

AstraZeneca

Environmental Assessment	
Drug Substance	Quetiapine
Document No.	CNS.000-030-693
Date	20 November 2002

Environmental Assessment of Quetiapine

Author: Gisela Holm, PhD
Ecotoxicologist
Global SHE Operations

TABLE OF CONTENTS **PAGE**

1. DATE

20 November, 2002

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 LP has filed an NDA pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Seroquel® 25 mg, 100 mg, 150 mg, 200 mg and 300 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 acute and chronic psychoses, including schizophrenia. An application has been filed to register Seroquel for use in acute bipolar mania.

4.3 Locations of use

Usage of Seroquel will occur in households, but also in hospitals throughout the United States.

4.4 Disposal sites

Empty or partially empty packages from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy, or clinic procedures.

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

See CMC module, Nomenclature and Structure.

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 or genus/species of biologic product (e.g., virus)

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.

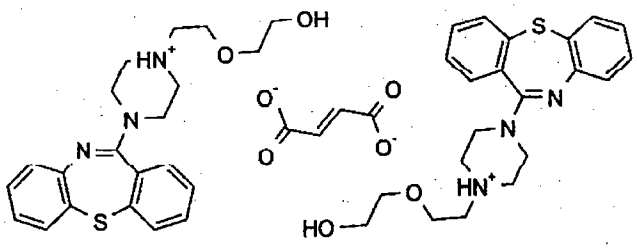
$C_{46}H_{54}N_6O_8S_2$ (quetiapine fumarate)
$C_{21}H_{25}N_3O_2S$ (base)

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/amino acid sequence



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**).

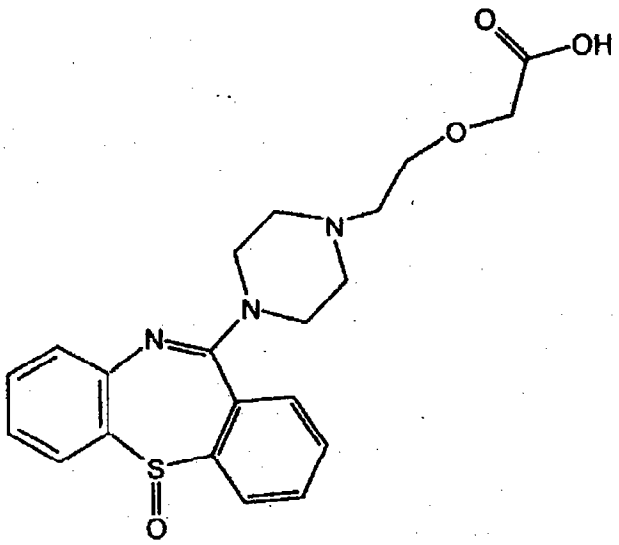


Figure 1. Structural formula for the sulfoxide acid metabolite (M 289,886).

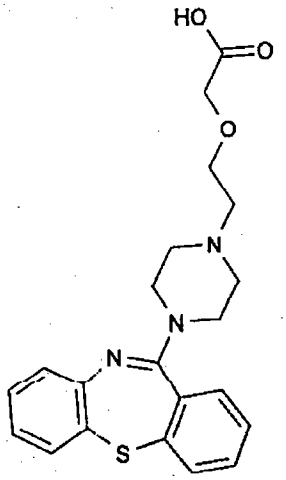


Figure 2. Structural formula for the parent acid metabolite (M 289,663).

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.

6.1.1.2 Physical and Chemical Characterization

Water solubility
1600 mg/L at pH 7 (Appendix II - **Confidential**)

Dissociation constants (pKa) (22°C)
(Appendix III – **Confidential**)

$pKa_1 = 6.8$
$pKa_2 = 3.3$

Octanol/Water Partition Coefficient (25°C)

$\log K_{ow} = 1.4$ at pH 5 (Appendix IV - **Confidential**)
$\log K_{ow} = 2.7$ at pH 7 (Appendix IV - **Confidential**)
$\log K_{ow} = 2.6$ at pH 9 (Appendix IV - **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 V - **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 VI - **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 III – **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 VII – **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 VIII – **Confidential**.

6.1.1.5 Summary of Environmental Fate

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 (NB screening test)

The respiration inhibition of activated sludge was assessed according to the Ecological and Toxicological Association of Dyestuffs Manufacturing Industries (ETAD) method 103 (Appendix IX - **Confidential**). No inhibition was observed at concentrations up to 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 X – **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 XI – **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 XII - **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 XIII - **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 XIV - **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 VIII - **Confidential**) = 19300/EIC >100 (assessment factor), and no effects were observed at MEEC, i.e. no further testing is needed.

6.1.3 Summary of Environmental Fate and Effects

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 VIII – **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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Testing laboratory:

Brixham Environmental Laboratory, AstraZeneca, Brixham, UK

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	
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)
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

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

Appendix I. Investigator's Brochure Seroquel™ (Quetiapine fumarate; ICI 204,636 fumarate). AstraZeneca Pharmaceuticals, Mereside, Alderley Park, UK. 7th edition, January 2002.

Appendix II. ICI 204,636 solubility measurements in partial fulfillment of FDA environmental-assessment requirements. Pharmaceutical research & development report no. SP3010/B. Zeneca Pharmaceuticals, Wilmington, USA. 22 September 1995.

Appendix III. Data generated in the US to support the environmental assessment report for ICI 204,636. Pharmaceutical research & development report no. SP2900/B. Zeneca Pharmaceuticals Group, Wilmington, USA. 29 March 1995.

Appendix IV. ICI 204,636 log partition coefficient measurements in partial fulfillment of FDA environmental assessment requirements. Pharmaceutical research &

development report no. SP3011/B. Zeneca Pharmaceuticals, Wilmington, USA. 3 October 1995.

Appendix V. Seroquel: Determination of 28 day ready biodegradability. Report no. BL5078/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix VI. Seroquel: Determination of anaerobic biodegradability. Report no. BL5077/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix VII. Seroquel: Soil sorption and adsorption. Report no. BL5062/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix VIII. Environmental concentrations of quetiapine. Document no. CNS.000-030-633, AstraZeneca Global SHE Operations, Södertälje, Sweden, 20 November, 2002.

Appendix IX. ICI 204636 PURE: Inhibition of the respiration rate of activated sludge by ETAD method 103. Report no. BLS1461/B. Brixham Environmental Laboratory (Former ICI Group Environmental Laboratory), Brixham, UK. December 1992.

Appendix X. Seroquel: Toxicity to the blue-green alga *Microcystis aeruginosa*. BL5018/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix XI. Seroquel: Toxicity to the green alga *Selenastrum capricornutum*. BL5017/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix XII. Seroquel: Chronic toxicity to *Daphnia magna*. BL5232/B. Brixham Environmental Laboratory, Brixham, UK. September 1994.

Appendix XIII. Seroquel: Acute toxicity to rainbow trout *Oncorhynchus mykiss*. BL5084/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix XIV. Seroquel: Acute toxicity to bluegill sunfish *Lepomis macrochirus*. BL5085/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

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/s/

Florian Zielinski
1/29/03 10:16:36 AM

Nancy Sager
1/30/03 04:26:51 PM

Yuan-Yuan Chiu
2/3/03 10:53:27 AM
Concurred

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

SEROQUEL® TABLETS
(quetiapine fumarate)

NDA 20-639 / S-016
Treatment of acute bipolar mania (mono-therapy)

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neurological Drug Products
(HFD-120)

January 28, 2003

Environmental Assessment Review #1, NDA 20-639 / S-016
SEROQUEL (quetiapine fumarate) TABLETS
Treatment of acute bipolar mania (mono-therapy)

EXECUTIVE SUMMARY

A FONSI is recommended

The environmental assessment (EA) dated Nov 20, 2002 and follow-up E-mail dated Jan 20, 2003 support the supplemental new drug application for a new indication, treatment of acute bipolar mania (mono-therapy). The EA was prepared in accordance with 21 CFR Part 25 by AstraZeneca Pharmaceuticals LP. The EA contains environmental fate and effects data resulting from the use and disposal of Seroquel (quetiapine fumarate) Tablets.

Quetiapine is almost completely eliminated by metabolism by the patient. Approximately 1% of the administered dose is excreted unchanged. Approximately 73% of the dose is excreted as metabolites in urine and 20% is excreted in feces. The two major metabolites (57% of the administered dose) were tested *in vivo* and neither showed any pharmacological activity in terms of binding affinity and behavioral tests of dopamine antagonists. It is assumed that approximately 43% of the administered dose is excreted as potential active metabolites and conjugates that have similar pharmacological activity as quetiapine for the purpose of estimating the EIC. These compounds may enter the aquatic environment from patient use and disposal. The log K_{OW} of quetiapine fumarate is less than 3.0 between pH 5 and pH 9. Rapid degradation is not expected.

Assuming that no metabolism occurs, the EIC of quetiapine fumarate is[ ] ppb.
(If *in-vivo* metabolism is included in the calculation, the EIC of quetiapine is[ ] ppb)

The toxicity of quetiapine fumarate to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

Test	Result
Microbial Growth Inhibition (ETAD Method 103)	No inhibition up to 100 ppm
Blue-green alga (M. aeruginosa) (21 day, TAD 4.01)	NOEC = 4 mg/L (max cell density) NOEC = 32 mg/L (growth rate)
Green alga (S. capricornutum) (14 day, TAD 4.01)	NOEC = 2.5 mg/L (max cell density & growth rate)
Rainbow Trout	NOEC = 1.0 ppm (96 hour) LC_{50} = 22.0 ppm (96 hour)
Bluegill Sunfish	NOEC = 1.8 ppm (96 hour) LC_{50} = 19.3 ppm (96 hour)
Daphnia magna (reproduction and length)	NOEC = 18 ppm (21 day) LOEC = 32 ppm (21 day)

REVIEW OF EA SUBMITTED IN NDA 20-639 / S-016

Treatment of acute bipolar mania (mono-therapy)

I. DATE: November 20, 2002 (Original submission)
January 20, 2003 (Follow-up E-mail)

II APPLICANT: AstraZeneca Pharmaceuticals LP

III ADDRESS: 1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

IV DESCRIPTION OF PROPOSED ACTION:

a. Requested Approval: AstraZeneca Pharmaceuticals LP has filed an NDA supplement pursuant to section 505 (b) of the FDA Act for Seroquel (quetiapine fumarate), 25 mg, 100 mg, 150 mg, 200 mg and 300 mg Tablets packaged in bottles and hospital unit dose packages. An EA has been submitted pursuant to 21 CFR part 25.
b. Need for Action: Supplemental application (NDA 20-639 / S-016) requests approval of quetiapine fumarate for use in treatment of acute bipolar mania (mono-therapy). Seroquel Tablets (quetiapine fumarate) are currently approved for treatment of acute and chronic psychoses, including schizophrenia.
c. Locations of Use: Hospitals, clinics and patient homes.
d. Disposal Sites: Empty or partially empty containers from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy 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.)

ADEQUATE

V IDENTIFICATION OF CHEMICALS

USAN Name: quetiapine fumarate
Brand Name: Seroquel Tablets

CAS Name: Ethanol{2-(2-[4-(dibenzo[b,f][1,4]-thiazepin-11-yl-1)piperazinyl)ethoxy}-(E)-2-butenedioate (2:1)

CAS Number: 111974-72-2 (quetiapine fumarate) Molecular Wt of $C_{46}H_{54}N_6O_8S_2$ is 883.1
111974-69-7 (free base) Molecular Wt of $C_{21}H_{25}N_3O_2S$ is 383.5

The molecular structure of quetiapine fumarate and the free base is in the EA, page 4.
Note that one molecule of quetiapine fumarate yields two molecules of the free base.

ADEQUATE

VI ENVIRONMENTAL ISSUES / Assessing Toxicity to Environmental Organisms

Information about environmental fate and effects is in the EA. Test reports are in the confidential appendix. Suitable scientific and GLP methodologies described in the confidential appendix were used to determine environmental fate and effects.

Environmental Fate:

Identification of Substances of Interest:
Quetiapine is almost completely eliminated by metabolism by the patient. Approximately 1% of the administered dose is excreted unchanged. Approximately 73% of the dose is excreted as metabolites in urine and 20% is excreted in feces. These compounds may enter the aquatic environment from patient use and disposal.

The two major metabolites (57% of the administered dose) were tested *in vivo* and neither showed any pharmacological activity in terms of binding affinity and behavioral tests of dopamine antagonists. It is assumed that approximately 43% of the administered dose is excreted as potential active metabolites and conjugates that have similar pharmacological activity as quetiapine for the purpose of estimating the EIC.

Physical and Chemical Characterization of quetiapine fumarate:
Quetiapine fumarate is very soluble in water (1600 mg/L at pH 7).
Dissociation Constants at 22°C are $pK_{a1} = 6.8$ and $pK_{a2} = 3.3$.
The log K_{OW} of quetiapine fumarate is less than 3.0 between pH 5 and 9.
Adsorption to Soil: Essentially immobile based on soil sorption / desorption testing.

Environmental Depletion Mechanisms:
Aerobic and Anaerobic Degradation: Rapid degradation was not observed
Hydrolysis: Not observed
Photolysis: Not observed

Environmental Concentrations:
The total quantity of quetiapine fumarate required for the new indication and all other products manufactured by AstraZeneca in any of the next 5 years is expected to be NMT [ ] (Reference: Current EA dated November 20, 2002, Confidential Appendix VIII).

Assuming that no metabolism occurs, the EIC of quetiapine fumarate is [ ] ppb.
(If *in-vivo* metabolism is included in the calculation, the EIC of quetiapine is [ ] ppb)

Summary of the Environmental Fate:
The drug substance, its metabolites and conjugates are expected to enter the aquatic environment.

Environmental Effects:

Inhibition of Activated Sludge: (ETAD Method 103)
Not observed at concentrations ≤ 100 mg / Liter.

Blue-Green Alga: 21-day, TAD 4.01
The NOEC based on specific growth rate is 32 mg/L
The lowest significant effect concentration based on specific growth rate is 64 mg/L
The NOEC based on maximum cell density is 4.0 mg/L
The lowest significant effect concentration based on maximum cell density is 8.0 mg/L

Green Alga: 14-day, TAD 4.01
The NOEC based on specific growth rate is 2.5 mg/L
The lowest significant effect concentration based on specific growth rate is 5.0 mg/L
The NOEC based on maximum cell density is 2.5 mg/L
The lowest significant effect concentration based on maximum cell density is 5.0 mg/L

Daphnia Magna: 21-day Reproduction and Length, TAD 4.09
The 21-day NOEC for daphnia magna is 18 ppm.
The 21-day LOEC for daphnia magna is 32 ppm.

These values are ≥1000 times greater than the EIC assuming no metabolism, namely[ ]ppb.
The EIC assuming no metabolism, namely[ ]ppb, is lower than the NOEC.

Rainbow Trout: TAD 4.11
The 96-hour LC_{50} for rainbow trout was 22.0 ppm.
The 96-hour NOEC for rainbow trout is 1.0 ppm.

The LC_{50} is ≥1000 times greater than the EIC assuming no metabolism, namely[ ]ppb.
The EIC assuming no metabolism, namely[ ]ppb, is lower than the NOEC.

Bluegill Sunfish: TAD 4.11
The 96-hour LC_{50} for bluegill sunfish is 19.3 ppm.
The 96-hour NOEC for bluegill sunfish is 1.8 ppm.

The LC_{50} is ≥1000 times greater than the EIC assuming no metabolism, namely[ ]ppb.
The EIC assuming no metabolism, namely[ ] ppb, is lower than the NOEC.

Summary of Environmental Effects:

The toxicity of quetiapine fumarate to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

Test	Result
Microbial Growth Inhibition (ETAD Method 103)	No inhibition up to 100 ppm
Blue-green alga (M. aeruginosa) (21 day, TAD 4.01)	NOEC = 4 mg/L (max cell density) NOEC = 32 mg/L (growth rate)
Green alga (S. capricornutum) (14 day, TAD 4.01)	NOEC = 2.5 mg/L (max cell density & growth rate)
Rainbow Trout	NOEC = 1.0 ppm (96 hour) LC_{50} = 22.0 ppm (96 hour)
Bluegill Sunfish	NOEC = 1.8 ppm (96 hour) LC_{50} = 19.3 ppm (96 hour)
Daphnia magna (reproduction and length)	NOEC = 18 ppm (21 day) LOEC = 32 ppm (21 day)

ADEQUATE

VII MITIGATION MEASURES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

VIII ALTERNATIVES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

IX PREPARERS

Names, job titles and qualifications were provided.

ADEQUATE

X CERTIFICATION

Certification of each test report is provided.

AstraZeneca (Patricia DeFeo) certified the entire EA by E-mail dated January 20, 2003. Certification was addressed to the FDA Project Manager (Doris Bates).

ADEQUATE

XI APPENDICES

Reports and production estimate are provided in Confidential Appendices

ADEQUATE

Review by: Florian Zielinski on January 28, 2003
Chemist, Center for Drug Evaluation and Research

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/s/

Florian Zielinski
1/30/03 03:31:36 PM
ENV ASSESSMENT

Nancy Sager
1/30/03 04:29:10 PM
ENV ASSESSMENT

Yuan-Yuan Chiu
2/3/03 10:48:35 AM
CHEMIST
Concurred

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

SEROQUEL® TABLETS
(quetiapine fumarate)

NDA 20-639 / S-017
Treatment of acute bipolar mania (adjunctive-therapy)

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neurological Drug Products
(HFD-120)

January 28, 2003

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-639 / S-017

SEROQUEL® TABLETS (quetiapine fumarate)
Treatment of acute bipolar mania (adjunctive-therapy)

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 has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

This supplement requests approval of Seroquel Tablets (quetiapine fumarate) for treatment of acute polar mania (adjunctive-therapy). In support of its supplemental 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 is a chemically synthesized drug currently approved for treatment of acute and chronic psychoses, including schizophrenia.

Quetiapine fumarate and its metabolites and conjugates may enter the aquatic environment from patient use and disposal. Quetiapine fumarate is not degraded by aerobic and anaerobic, hydrolytic and photolytic mechanisms. 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
Florian Zielinski
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Nancy B. Sager
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Yuan-yuan Chiu, Ph.D.
Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

AstraZeneca

Environmental Assessment	
Drug Substance	Quetiapine
Document No.	CNS.000-030-693
Date	20 November 2002

Environmental Assessment of Quetiapine

Author: Gisela Holm, PhD
Ecotoxicologist
Global SHE Operations

TABLE OF CONTENTS **PAGE**

1. DATE

20 November, 2002

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 LP has filed an NDA pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Seroquel® 25 mg, 100 mg, 150 mg, 200 mg and 300 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 acute and chronic psychoses, including schizophrenia. An application has been filed to register Seroquel for use in *acute bipolar mania*.

4.3 Locations of use

Usage of Seroquel will occur in households, but also in hospitals throughout the United States.

4.4 Disposal sites

Empty or partially empty packages from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy, or clinic procedures.

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

See CMC module, Nomenclature and Structure.

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 or genus/species of biologic product (e.g., virus)

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.

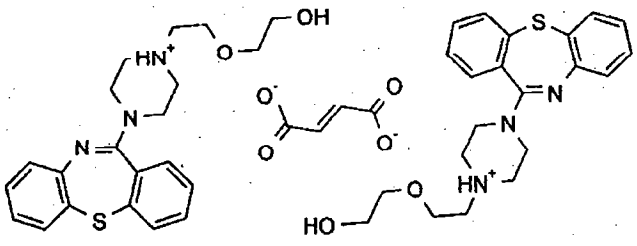
$C_{46}H_{54}N_6O_8S_2$ (quetiapine fumarate)
$C_{21}H_{25}N_3O_2S$ (base)

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/amino acid sequence



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**).

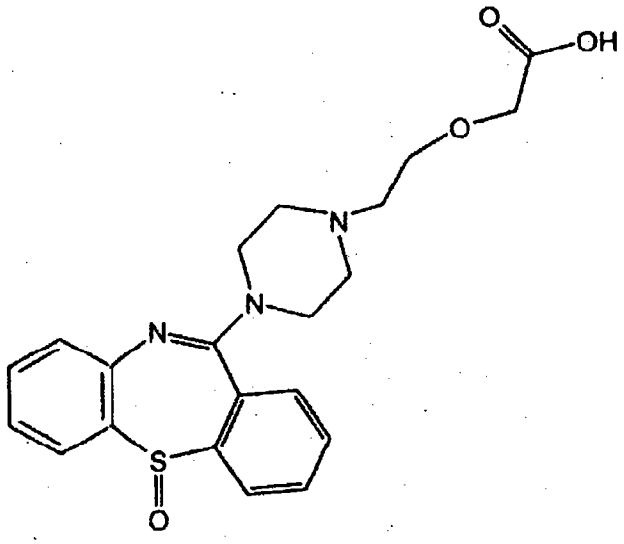


Figure 1. Structural formula for the sulfoxide acid metabolite (M 289,886).

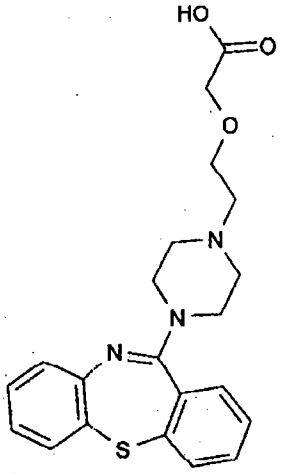


Figure 2. Structural formula for the parent acid metabolite (M 289,663).

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.

6.1.1.2 Physical and Chemical Characterization

Water solubility
1600 mg/L at pH 7 (Appendix II - **Confidential**)

Dissociation constants (pKa) (22°C)
(Appendix III – **Confidential**)

$pKa_1 = 6.8$
$pKa_2 = 3.3$

Octanol/Water Partition Coefficient (25°C)

$\log K_{ow} = 1.4$ at pH 5 (Appendix IV - **Confidential**)
$\log K_{ow} = 2.7$ at pH 7 (Appendix IV - **Confidential**)
$\log K_{ow} = 2.6$ at pH 9 (Appendix IV - **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 V - **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 VI - **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 III – **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 VII – **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 VIII – **Confidential**.

6.1.1.5 Summary of Environmental Fate

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 (NB screening test)

The respiration inhibition of activated sludge was assessed according to the Ecological and Toxicological Association of Dyestuffs Manufacturing Industries (ETAD) method 103 (Appendix IX - **Confidential**). No inhibition was observed at concentrations up to 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 X – **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 XI – **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 XII - **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 XIII - **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 XIV - **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 VIII - **Confidential**) = 19300/EIC >100 (assessment factor), and no effects were observed at MEEC, i.e. no further testing is needed.

6.1.3 Summary of Environmental Fate and Effects

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 VIII – **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

Gisela Holm, Ecotoxicologist, Global SHE Operations, AstraZeneca, Södertälje, Sweden since six years, Ph.D. Stockholm University, 15 years of experience in environmental research and consulting.

Persons consulted:

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Donna Caster, Manager, AstraZeneca Pharmaceuticals LP, Wilmington, USA
Ghanshyam (Gus) Patel, Senior Scientist, AstraZeneca Pharmaceuticals LP, Wilmington, USA
Norb Ealer, Associate Director, Technical Regulatory Affairs AstraZeneca Pharmaceuticals LP, Wilmington, USA
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Helen Winter Ph.D. Associate Director, Clinical Pharmacokinetics, Experimental Medicine, AstraZeneca Pharmaceuticals LP, Wilmington, USA

Testing laboratory:

Brixham Environmental Laboratory, AstraZeneca, Brixham, UK

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	
[illegible]	
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)
[illegible]	
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

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

Appendix I. Investigator's Brochure Seroquel™ (Quetiapine fumarate; ICI 204,636 fumarate). AstraZeneca Pharmaceuticals, Mereside, Alderley Park, UK. 7th edition, January 2002.

Appendix II. ICI 204,636 solubility measurements in partial fulfillment of FDA environmental-assessment requirements. Pharmaceutical research & development report no. SP3010/B. Zeneca Pharmaceuticals, Wilmington, USA. 22 September 1995.

Appendix III. Data generated in the US to support the environmental assessment report for ICI 204,636. Pharmaceutical research & development report no. SP2900/B. Zeneca Pharmaceuticals Group, Wilmington, USA. 29 March 1995.

Appendix IV. ICI 204,636 log partition coefficient measurements in partial fulfillment of FDA environmental assessment requirements. Pharmaceutical research &

development report no. SP3011/B. Zeneca Pharmaceuticals, Wilmington, USA. 3 October 1995.

Appendix V. Seroquel: Determination of 28 day ready biodegradability. Report no. BL5078/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix VI. Seroquel: Determination of anaerobic biodegradability. Report no. BL5077/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix VII. Seroquel: Soil sorption and adsorption. Report no. BL5062/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix VIII. Environmental concentrations of quetiapine. Document no. CNS.000-030-633, AstraZeneca Global SHE Operations, Södertälje, Sweden, 20 November, 2002.

Appendix IX. ICI 204636 PURE: Inhibition of the respiration rate of activated sludge by ETAD method 103. Report no. BLS1461/B. Brixham Environmental Laboratory (Former ICI Group Environmental Laboratory), Brixham, UK. December 1992.

Appendix X. Seroquel: Toxicity to the blue-green alga *Microcystis aeruginosa*. BL5018/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix XI. Seroquel: Toxicity to the green alga *Selenastrum capricornutum*. BL5017/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix XII. Seroquel: Chronic toxicity to *Daphnia magna*. BL5232/B. Brixham Environmental Laboratory, Brixham, UK. September 1994.

Appendix XIII. Seroquel: Acute toxicity to rainbow trout *Oncorhynchus mykiss*. BL5084/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix XIV. Seroquel: Acute toxicity to bluegill sunfish *Lepomis macrochirus*. BL5085/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

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/s/

Florian Zielinski
1/29/03 10:19:23 AM

Nancy Sager
1/30/03 04:27:54 PM

Yuan-Yuan Chiu
2/3/03 10:55:04 AM
Concurred

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

SEROQUEL® TABLETS
(quetiapine fumarate)

NDA 20-639 / S-017
Treatment of acute bipolar mania (adjunctive-therapy)

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neurological Drug Products
(HFD-120)

January 28, 2003

Environmental Assessment Review #1, NDA 20-639 / S-017
SEROQUEL (quetiapine fumarate) TABLETS
Treatment of acute bipolar mania (adjunctive-therapy)

EXECUTIVE SUMMARY

A FONSI is recommended

The environmental assessment (EA) dated Nov 20, 2002 and follow-up E-mail dated Jan 20, 2003 support the supplemental new drug application for a new indication, treatment of acute bipolar mania (adjunctive-therapy). The EA was prepared in accordance with 21 CFR Part 25 by AstraZeneca Pharmaceuticals LP. The EA contains environmental fate and effects data resulting from the use and disposal of Seroquel (quetiapine fumarate) Tablets.

Quetiapine is almost completely eliminated by metabolism by the patient. Approximately 1% of the administered dose is excreted unchanged. Approximately 73% of the dose is excreted as metabolites in urine and 20% is excreted in feces. The two major metabolites (57% of the administered dose) were tested *in vivo* and neither showed any pharmacological activity in terms of binding affinity and behavioral tests of dopamine antagonists. It is assumed that approximately 43% of the administered dose is excreted as potential active metabolites and conjugates that have similar pharmacological activity as quetiapine for the purpose of estimating the EIC. These compounds may enter the aquatic environment from patient use and disposal. The log K_{OW} of quetiapine fumarate is less than 3.0 between pH 5 and pH 9. Rapid degradation is not expected.

Assuming that no metabolism occurs, the EIC of quetiapine fumarate is[ ] ppb.
(If *in-vivo* metabolism is included in the calculation, the EIC of quetiapine is[ ] ppb)

The toxicity of quetiapine fumarate to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

Test	Result
Microbial Growth Inhibition (ETAD Method 103)	No inhibition up to 100 ppm
Blue-green alga (M. aeruginosa) (21 day, TAD 4.01)	NOEC = 4 mg/L (max cell density) NOEC = 32 mg/L (growth rate)
Green alga (S. capricornutum) (14 day, TAD 4.01)	NOEC = 2.5 mg/L (max cell density & growth rate)
Rainbow Trout	NOEC = 1.0 ppm (96 hour) LC_{50} = 22.0 ppm (96 hour)
Bluegill Sunfish	NOEC = 1.8 ppm (96 hour) LC_{50} = 19.3 ppm (96 hour)
Daphnia magna (reproduction and length)	NOEC = 18 ppm (21 day) LOEC = 32 ppm (21 day)

REVIEW OF EA SUBMITTED IN NDA 20-639 / S-017

Treatment of acute bipolar mania (adjunctive-therapy)

I. DATE: November 20, 2002 (Original submission)
January 20, 2003 (Follow-up E-mail)

II APPLICANT: AstraZeneca Pharmaceuticals LP

III ADDRESS: 1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

IV DESCRIPTION OF PROPOSED ACTION:

a. Requested Approval: AstraZeneca Pharmaceuticals LP has filed an NDA supplement pursuant to section 505 (b) of the FDA Act for Seroquel (quetiapine fumarate), 25 mg, 100 mg, 150 mg, 200 mg and 300 mg Tablets packaged in bottles and hospital unit dose packages. An EA has been submitted pursuant to 21 CFR part 25.
b. Need for Action: Supplemental application (NDA 20-639 / S-017) requests approval of quetiapine fumarate for use in treatment of acute bipolar mania (adjunctive-therapy). Seroquel Tablets (quetiapine fumarate) are currently approved for treatment of acute and chronic psychoses, including schizophrenia.
c. Locations of Use: Hospitals, clinics and patient homes.
d. Disposal Sites: Empty or partially empty containers from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy 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.)

ADEQUATE

V IDENTIFICATION OF CHEMICALS

USAN Name: quetiapine fumarate
Brand Name: Seroquel Tablets

CAS Name: Ethanol{2-(2-[4-(dibenzo[b,f][1,4]-thiazepin-11-yl-1)piperazinyl)ethoxy}-(E)-2-butenedioate (2:1)

CAS Number: 111974-72-2 (quetiapine fumarate) Molecular Wt of $C_{46}H_{54}N_6O_8S_2$ is 883.1
111974-69-7 (free base) Molecular Wt of $C_{21}H_{25}N_3O_2S$ is 383.5

The molecular structure of quetiapine fumarate and the free base is in the EA, page 4.
Note that one molecule of quetiapine fumarate yields two molecules of the free base.

ADEQUATE

VI ENVIRONMENTAL ISSUES / Assessing Toxicity to Environmental Organisms

Information about environmental fate and effects is in the EA. Test reports are in the confidential appendix. Suitable scientific and GLP methodologies described in the confidential appendix were used to determine environmental fate and effects.

Environmental Fate:

Identification of Substances of Interest:
Quetiapine is almost completely eliminated by metabolism by the patient. Approximately 1% of the administered dose is excreted unchanged. Approximately 73% of the dose is excreted as metabolites in urine and 20% is excreted in feces. These compounds may enter the aquatic environment from patient use and disposal.

The two major metabolites (57% of the administered dose) were tested *in vivo* and neither showed any pharmacological activity in terms of binding affinity and behavioral tests of dopamine antagonists. It is assumed that approximately 43% of the administered dose is excreted as potential active metabolites and conjugates that have similar pharmacological activity as quetiapine for the purpose of estimating the EIC.

Physical and Chemical Characterization of quetiapine fumarate:
Quetiapine fumarate is very soluble in water (1600 mg/L at pH 7).
Dissociation Constants at 22°C are $pK_{a1} = 6.8$ and $pK_{a2} = 3.3$.
The log K_{OW} of quetiapine fumarate is less than 3.0 between pH 5 and 9.
Adsorption to Soil: Essentially immobile based on soil sorption / desorption testing.

Environmental Depletion Mechanisms:
Aerobic and Anaerobic Degradation: Rapid degradation was not observed
Hydrolysis: Not observed
Photolysis: Not observed

Environmental Concentrations:
The total quantity of quetiapine fumarate required for the new indication and all other products manufactured by AstraZeneca in any of the next 5 years is expected to be NMT [redacted]
(Reference: Current EA dated November 20, 2002, Confidential Appendix VIII).

Assuming that no metabolism occurs, the EIC of quetiapine fumarate is [redacted] ppb.
(If *in-vivo* metabolism is included in the calculation, the EIC of quetiapine is [redacted] ppb)

Summary of the Environmental Fate:
The drug substance, its metabolites and conjugates are expected to enter the aquatic environment.

Environmental Effects:

Inhibition of Activated Sludge: (ETAD Method 103)
Not observed at concentrations ≤ 100 mg / Liter.

Blue-Green Alga: 21-day, TAD 4.01
The NOEC based on specific growth rate is 32 mg/L
The lowest significant effect concentration based on specific growth rate is 64 mg/L
The NOEC based on maximum cell density is 4.0 mg/L
The lowest significant effect concentration based on maximum cell density is 8.0 mg/L

Green Alga: 14-day, TAD 4.01
The NOEC based on specific growth rate is 2.5 mg/L
The lowest significant effect concentration based on specific growth rate is 5.0 mg/L
The NOEC based on maximum cell density is 2.5 mg/L
The lowest significant effect concentration based on maximum cell density is 5.0 mg/L

Daphnia Magna: 21-day Reproduction and Length, TAD 4.09
The 21-day NOEC for daphnia magna is 18 ppm.
The 21-day LOEC for daphnia magna is 32 ppm.

These values are ≥1000 times greater than the EIC assuming no metabolism, namely [redacted] ppb.
The EIC assuming no metabolism, namely [redacted] ppb, is lower than the NOEC.

Rainbow Trout: TAD 4.11
The 96-hour LC_{50} for rainbow trout was 22.0 ppm.
The 96-hour NOEC for rainbow trout is 1.0 ppm.

The LC_{50} is ≥1000 times greater than the EIC assuming no metabolism, namely [redacted] ppb.
The EIC assuming no metabolism, namely [redacted] ppb, is lower than the NOEC.

Bluegill Sunfish: TAD 4.11
The 96-hour LC_{50} for bluegill sunfish is 19.3 ppm.
The 96-hour NOEC for bluegill sunfish is 1.8 ppm.

The LC_{50} is ≥1000 times greater than the EIC assuming no metabolism, namely [redacted] ppb.
The EIC assuming no metabolism, namely [redacted] ppb, is lower than the NOEC.

Summary of Environmental Effects:

The toxicity of quetiapine fumarate to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

Test	Result
Microbial Growth Inhibition (ETAD Method 103)	No inhibition up to 100 ppm
Blue-green alga (M. aeruginosa) (21 day, TAD 4.01)	NOEC = 4 mg/L (max cell density) NOEC = 32 mg/L (growth rate)
Green alga (S. capricornutum) (14 day, TAD 4.01)	NOEC = 2.5 mg/L (max cell density & growth rate)
Rainbow Trout	NOEC = 1.0 ppm (96 hour) LC_{50} = 22.0 ppm (96 hour)
Bluegill Sunfish	NOEC = 1.8 ppm (96 hour) LC_{50} = 19.3 ppm (96 hour)
Daphnia magna (reproduction and length)	NOEC = 18 ppm (21 day) LOEC = 32 ppm (21 day)

ADEQUATE

VII MITIGATION MEASURES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

VIII ALTERNATIVES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

IX PREPARERS

Names, job titles and qualifications were provided.

ADEQUATE

X CERTIFICATION

Certification of each test report is provided.

AstraZeneca (Patricia DeFeo) certified the entire EA by E-mail dated January 20, 2003. Certification was addressed to the FDA Project Manager (Doris Bates).

ADEQUATE

XI APPENDICES

Reports and production estimate are provided in Confidential Appendices

ADEQUATE

Review by: Florian Zielinski on January 28, 2003
Chemist, Center for Drug Evaluation and Research

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

/s/

Florian Zielinski
1/30/03 03:34:06 PM
ENV ASSESSMENT

Nancy Sager
1/30/03 04:30:55 PM
ENV ASSESSMENT

Yuan-Yuan Chiu
2/3/03 10:51:57 AM
CHEMIST
Concurred

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-639/S-016 & S-017

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-639/ SE1-016 & SE1-017.
Drug Name	Seroquel (Quetiapine) 400-800 mg/Day. Supplied in tablets of 25, 100 and 200 mg.
Indication(s):	Acute mania in Patients With Bipolar Disorder: As Monotherapy (SE1-0116) and as Adjunct Therapy (SE1-017).
Applicant:	AstraZeneca.
Date(s):	Date received by CDER: 01/10/2003. PDUFA Date: 11/01/203.
Review Status:	Standard, 6S.
Biometrics Division:	Division of Biometrics I.
Statistical Reviewer:	Kooros Mahjoob, Ph.D.
Concurring Reviewers:	Team Leader: Kun Jin, Ph.D. Division Director: George Chi, Ph.D.
Medical Division:	Division of Neuropharmacological Drug Products (HFD-120)
Clinical Team:	Clinical Reviewer: Robert Levin, MD. Clinical Team Leader: Thomas Laughren Clinical Division Director: Russell Katz
Project Manager:	Doris Bates, Ph.D.

Keywords: Seroquel, Monotherapy, Adjunct Therapy, Primary Efficacy, ANCOVA, LOCF and MMRM

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The NDA 20-639 is a supplemental submission on Seroquel (generic Name: **Quetiapine**) for the treatment of acute mania for patients with bipolar disorder. The submission contains data to support the use of the drug as a monotherapy as well as an adjunct therapy.

1.1 CONCLUSIONS AND RECOMMENDATIONS

Based on the results of the statistical analyses of the efficacy data of the two monotherapy and two adjunct therapy studies presented the sponsor and the results of analysis performed by this reviewer, the following are concluded.

1.1.1 Monotherapy

The efficacy results presented by the sponsor, as well as the results of analyses performed by this reviewer, on the data of the two randomized placebo controlled studies (IL/0104 & IL/0105) indicate that, in both Studies, Quetiapine, when used as a monotherapy in the treatment of acute mania associated with bipolar disorder, is effective and is statistically significantly superior to placebo (See Tables 3 & 5). Hence, the two studies provide the statistical support for the efficacy claim.

1.1.2 Adjunct Therapy

The efficacy results presented by the sponsor, as well as the results of analyses performed by this reviewer, on the data of the two randomized placebo controlled studies (IL/0099 & IL/0100) indicate that: in Study IL/0099, Quetiapine, when used as an adjunct therapy in the treatment of acute mania associated with bipolar disorder, is effective and is statistically significantly superior to placebo. However, the result from Study IL/0100 failed to show effectiveness of Quetiapine over placebo (see Tables 4 & 6).

Overall, for both monotherapy studies the results are in favor of Quetiapine over placebo. With respect to the two adjunct therapy studies, one of the studies failed to demonstrate the efficacy, the results of the analyses presented by the applicant and well as those performed by this reviewer support the efficacy of Quetiapine for treatment of acute mania associated with bipolar disorder.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Quetiapine was registered in the United Kingdom in July 1997, followed by the FDA in September 1997, for the treatment of psychosis/schizophrenia.

In the schizophrenia studies, Quetiapine has established a good safety and tolerability profile. Therefore, because of known overlap between the symptoms of schizophrenia and acute mania, the therapy with Quetiapine could provide efficacy with a better tolerability over the other treatments, for the treatment of acute mania associated with bipolar disorder.

The clinical development program consisted of four studies on Quetiapine to evaluate the safety and efficacy of the drug in treatment of acute mania associated with bipolar disorder. Two of these studies, IL/0104 and IL/0105, assess its effectiveness as a monotherapy (data is submitted as the Serial No. SE1-016) and the other two studies, IL/0099 and IL/0100 (data is submitted as the Serial No. SE1-017), assessing its effectiveness as an adjunct to mood stabilizers (lithium or Divalproex).

The objectives across all four studies were to address the key treatment goals of assessing Quetiapine as monotherapy and/or adjunct therapy with respect to:

- Effectiveness in treating acute mania (primary objective).
- Effectiveness in treating depressive symptoms, psychotic symptoms of patients with psychotic symptoms at baseline, agitation and aggression, and to improve functional status.
- Safety and tolerability, across all four studies, in the treatment of acute mania.

All studies employed similar entry criteria, dosing regimen, efficacy endpoints and safety assessments.

Patients were male/female hospitalize with DSM-IV diagnosis of bipolar I disorder, of age 18 years or older, at screening and at randomization having a minimum score of 20 on the YMRS. There were also other entry-criteria, which will be presented where detail review is given.

A brief description to the design, dosage and other information on monotherapy and adjunct therapy studies is presented below.

1.2.1 Monotherapy Studies

1.2.1.1 Design

Both studies were designed as multicenter (multinational), double-blind, randomized, parallel-group, placebo-controlled, 12-week studies to compare, mainly, the effects of Quetiapine with placebo. Also, each study had an additional active treatment arm as comparators: Haloperidol in Study IL/0204 and Lithium in Study IL/0105. These two studies were conducted in sites located in the countries in Asia and Europe. There **were no United States sites** in either of these two studies.

1.2.1.2 Patients Disposition

A total of 302 patients were randomized in each of the two studies. The efficacy assessment was based on the Modified Intent to Treat (**MITT**) patients, which includes all randomized patients who took study medication and who had baseline and at least 1 set of post-baseline YMRS assessments.

The following table gives the number of patients at randomization, discontinued, and MITT in each treatment group for the two studies.

Table 1. (***Monotherapy Studies***): Number of Patients Randomized and Discontinued By Treatment

Study	Patient Population	Treatment				Total
		Quetiapine	Placebo	Haloperidol	Lithium	
IL/0104	Randomized	102	101	99	[redacted]	302
	MITT†	101	100	98	[redacted]	299
	Discontinued Day 21†	21 (21%)	27 (27%)	12 (12%)	[redacted]	60 (20)
	Discontinued Day 84†	46 (46%)	58 (58%)	44 (45%)	[redacted]	151 (50%)
IL/0105	Randomized	107	97	[redacted]	98	302
	MITT†	107	95	[redacted]	98	300
	Discontinued Day 21†	5 (5%)	16 (17%)	[redacted]	10 (10%)	31 (10%)
	Discontinued Day 84†	33 (31%)	60 (63%)	[redacted]	31 (32%)	124 (41%)

†: Percentages are relative to the number of patients in MITT population.

Table 1 shows that, between the two studies, for the Day 21, the discontinuation rates for the MITT patient population are as high as 21% for Quetiapine, 27% for placebo, 12% for Haloperidol and 10% for Lithium these percentages are relatively moderate. However, for the Day 84, the rate is as high as 46% for Quetiapine and 58% for placebo.

1.2.1.3 Dosage

Quetiapine dosing was initiated at 100 mg/day on Day 1 increasing to 400 mg/day on Day 4 in increments of 100 mg/day. The Quetiapine dose could be adjusted to between 200 and 600 mg/day on Day 5, and to between 200 and 800 mg/day on Days 6 to 84, based on efficacy and/or tolerability issues.

In Study IL/0104 haloperidol dosing was initiated at 2 mg/day. The range was between 2 and 8 mg/day on Days 6 to 84, based on efficacy and/or tolerability issues.

In Study IL/0105 lithium dosing was initiated on Day 1 at a dose of 900 mg/day. Dose adjustment between Days 5 and 84 was at the discretion of the dosing investigator in order to achieve symptom control and/or minimize side effects issues.

1.2.1.4 Endpoints

For both studies the primary endpoint was change at Day 21 from baseline (Day 1) in YMRS Total score (**CT_YMRS**). The secondary endpoints include, CT_YMRS at Day 84, YMRS response rate, time to respond YMRS emission rate and Change from baseline in MADRS score.

1.2.2 Adjunct Therapy Studies

1.2.2.1 Design

Both IL/0099 and IL/0100 studies were designed as multicenter, double-blind, randomized, parallel-group, placebo-controlled studies. The Quetiapine was added as an adjunct to the mood stabilizers (lithium or Divalproex).

The duration of randomized treatment was 21 days in Study IL/0099 and 42 days in Study IL/0100. Study IL/0099 was conducted in the United States and Study IL/0100 was conducted in Canada, Europe, India and South Africa.

1.2.2.2 Patient Disposition

A total of 191 and 209 patients were randomized in studies IL/009 and IL/0100, respectively. The efficacy assessment was based on the Modified Intent to Treat (**MITT**) patients that includes all randomized patients who had baseline, took study medication and had at least one post-baseline YMRS assessments.

Table 2 gives the number of patients at randomization, discontinued, and MITT in each treatment group for the two studies.

Table 2. (***Adjunct Therapy Studies***): Number of Patients Randomized and Discontinued By Treatment

Study	Patient Population	Treatment Arm		Total
		Quetiapine	Placebo	
IL/0099	Randomized	91	100	191
	MITT†	81	89	170
	Discontinued Day 21†	34 (42%)	51 (57%)	79 (46%)
	Discontinued Day 42†			
IL/0100	Randomized	106	103	209
	MITT†	106	103	209
	Discontinued Day 21†	20 (19%)	19 (18%)	39 (19%)
	Discontinued Day 42†	35 (33%)	41 (40%)	76 (36%)

†: Percentages are relative to the number of patients in MITT population.

Table 2 shows that, fir Study 0100, the discontinuation rates at Day 21 is 19% for Quetiapine and 18% for placebo, which are moderate. However, the rates are as high as 42% for Quetiapine, 57% for placebo in Study IL/0099.

1.2.2.3 Dosage

Quetiapine dosing was initiated at 100 mg/day on Day 1 increasing to 400 mg/day on Day 4 in increments of 100 mg/day. The Quetiapine dose could be adjusted to between 200 and 600 mg/day on Day 5, and to between 200 and 800 mg/day on Days 6 to 21 for study IL/0099 and on Days 6 to 42 for Study IL/0100, based on efficacy and/or tolerability issues.

1.2.2.4 Endpoints

For both studies the primary endpoint was change at Day 21 from baseline (Day 1) in YMRS Total score (**T_YMRS**). The secondary endpoints include YMRS response rate, time to respond YMRS emission rate and Change from baseline in MADRS score. The assessment for the secondary endpoints was made at Day 21 for Study IL/0099 and at Day 21 and 42 for Study IL/0100.

1.3 STATISTICAL ISSUES AND FINDINGS

1.3.1 Sponsor's Analysis

For all four studies, the **analysis of covariance** (**ANCOVA**) was used to analyze the primary and secondary efficacy variables. The models used **change from baseline** as the **dependent** variable, **baseline** as the **covariate**, **treatment** as **fixed** effect and **center** as the **random** effect. Further ANCOVA was conducted for the combined data of the two studies, within each monotherapy and adjunct therapy. Missing values were replaced by last observation carried forward (**LOCF**) method (see Footnote 1, page 12).

Cochran-Mantel-Haenszel test was used for the analysis of binary response variables.

1.3.1.1 Monotherapy Results

Table 3 presents a summary of the sponsor's results on the change from baseline in T_YMRS (**CT_YMRS**).

Table 3. ***(Monotherapy Studies)*:** Summary of Sponsor's Efficacy Results on CT_YMRS[$]

Attribute	Study IL/0104						Study IL/0105					
	Number of Patients In Treatments (MITT)			Comparisons P-Values			Number of Patients In Treatments (MITT)			Comparisons P-Values		
	QTP	PLA	HAL	QTP vs. PLA	HAL vs. PLA	QTP vs. HAL	QTP	PLA	LIT	QTP Vs. PLA	LIT vs. PLA	QTP vs. LIT
N (MITT)	101	100	98				107	95	98			
Day 21 (P-Val)				**0.0096**	**<0.0001**	**SIG**				**<0.0001**	**<0.0001**	N-SIG
Day 84 (P-Val)				**<0.0001**	**<0.0001**	N-SIG				**<0.0001**	**<0.0001**	N-SIG

$: The entries are extracted from Tables 9 and 12 of the review; see those tables for more detail.

Table 3 shows that for both studies at Day 21: Quetiapine is statistically significantly superior to placebo (P<0.0001); Haloperidol and Lithium are statistically significantly superior to placebo (P<0.0001); Haloperidol is superior to Quetiapine but no statistical significant difference between Quetiapine and Lithium.

1.3.1.2 Adjunct Therapy Results

Table 4 presents a summary of the sponsor's results on CT_YMRS.

Table 4. ***(Adjunct Therapy Studies)***: Summary of Sponsor's Efficacy Results on CT_YMRS[$]

Day of Assessment Attribute	Study IL/0099			Study IL/0100		
	Number of Patients In Treatments (MITT)		Comparisons P-Values	Number of Patients In Treatments (MITT)		Comparisons P-Values
	QTP[†]	PLA[†]	QTP vs. PLA	QTP[†]	PLA[†]	QTP vs. PLA
N (MITT)	81	89		104	96	
Day 21 P-Value			0.0209			0.2809
Day. 42 P-Value						N-SIG

$: The entries are extracted from Tables 16 and 19; see those tables for more detail.
†: The Quetiapine and placebo treatments were added as adjunct to Lithium or Divalproex.

Table 4 shows that for Study IL/0099, Quetiapine is statistically significantly superior to placebo (P =0.0209). However, Study IL/0100 failed to show statistical superiority of Quetiapine over placebo.

1.3.2 Reviewer's Analysis

As an **alternative** to the sponsor's **primary** analysis of **ANCOVA** using LOCF, for both studies within the monotherapy and adjunct therapy, this reviewer used a "Mixed-Effects Model, Repeated Measure Approach" (**MMRM**) to analyze the data on T-YMRS. The model used change from baseline as the dependent variable, baseline as the covariate, visit and Treatment-by-Visit interaction. The results are given in the following tables (see Footnote 2, page 12).

1.3.2.1 Monotherapy Results

Table 5 presents a summary of the reviewer's results on the variable CT_YMRS.

Table 5. ***(Monotherapy Studies)***: Summary of Reviewers Efficacy Results on CT_YMRS[$]

Attribute	Study IL/0104						Study IL/0105					
	Number of Patients In Treatments (MITT)			Comparisons P-Values			Number of Patients In Treatments (MITT)			Comparisons P-Values		
	QTP	PLA	HAL	QTP vs. PLA	HAL vs. PLA	QTP vs. HAL	QTP	PLA	LIT	QTP Vs. PLA	LIT vs. PLA	QTP vs. LIT
N (MITT)	101	100	98				107	95	98			
Day 21 (P-Val)				0.0089	<0.0001	0.0783				<0.0001	<0.0001	0.3979
Day 84 (P-Val)				<0.0001	<0.0001	0.4478				<0.0001	<0.0001	0.2344

$: The entries are extracted from Tables 10 and 13; see those tables for more detail.
†: The Quetiapine and placebo treatments were added as adjunct to Lithium or Divalproex.

The comparison of results in Table 5 and those in Table 3 show that ANCOVA used by the sponsor and the MMRM used by this reviewer have produced, virtually, **similar** results leading to the same conclusion. So, the results are **robust** against the use of the two methodologies.

1.3.2.2 Adjunct Therapy Results

Table 6 presents a summary of the reviewer's results on the variable CT_YMRS.

Table 6. ***(Adjunct Therapy Studies)***: Summary of Reviewers Efficacy Results on CT_YMRS

Day of Assessment Attribute	Study IL/0099			Study IL/0100		
	Number of Patients In Treatments (MITT)		Comparisons P-Values	Number of Patients In Treatments (MITT)		Comparisons P-Values
	QTP[†]	PLA[†]	QTP vs. PLA	QTP[†]	PLA[†]	QTP vs. PLA
N (MITT)	81	89		104	96	
Day 21 P-Value			**0.0025**			0.6244
Day. 42 P-Value						0.5070

The entries are extracted from Tables 17 & 20; see those tables for more detail.

The comparison of results in Table 6 and those in Table 4 show that ANCOVA used by the sponsor and the MMRM used by this reviewer have produced, virtually, **similar** results leading to the same conclusion. So, the results are **robust** against the use of the two methodologies.

1.3.3 Statistical Issues

A potential issue could be use of inappropriate statistical analysis for handling the missing values and as a result introducing bias in the results. For, three of the four studies, as Tables 1 and 2 (also see Tables 8, 11, 15 & 18 and Figures 1-4) show, for the Day 1, the percentage of dropouts are in the rages of 12% to 27%, 5% to 17% and 18% to 19% for Studies IL/0104, IL/0105 and IL/0104, respectively. These rates are moderate, and hence the potential bias could be ignorable. However, the dropout rates for the US Study IL/0099 are in the rage of 35% to 57%; which is high. This can be an issue for the efficacy assessment of this study. However, ANCOVA and MMRM analysis have produced **similar** results. Therefore, the results are **robust** against the use of the two methodologies. The reader may read Section 5.1 for more detail.

1.3.4 Overall Findings

Overall, the results of the **primary analysis**, performed by the sponsor, and the **alternative analysis**, performed by this reviewer indicate that, the two monotherapy studies IL/00104 and IL/0105 and the adjunct therapy Study IL/0099 sufficiently support the superiority of Quetiapine over placebo in treatment of patients with acute mania associated with bipolar disorder. Although, the adjunct therapy IL/0100 failed to provide statistically significant results in favor of Quetiapine, however, numerically the results are in favor of Quetiapine.

NOTE: *The efficacy conclusion, in this review, is primarily based on the sponsor's ANCOVA, the* ***primary analysis****, results. The reviewer's MMRM analysis results are used as* ***supportive*** *analysis. The supportive analysis confirms the results of primary analysis.*

2 INTRODUCTION

2.1 OVERVIEW

Bipolar I disorder is a complex lifelong mental disease, which affects between 1% and 2% of the world's population. It is characterized by debilitating mood swings from intense euphoria to depression. There is a high risk of 10 to 15% suicides associated with the individuals with this disease. In addition, manic episodes in bipolar disorder are associated with depressive symptoms, psychosis and functional impairment, all of which can require hospitalization. Manic episodes are associated with agitated, aggressive and impulsive behavior, putting patients and those around them at considerable risk.

2.1.1 History and Rational for Research and Development

Quetiapine was registered in the United Kingdom in July 1997, followed by the FDA in September 1997, for the treatment of psychosis/schizophrenia.

As stated in the submission, presently, there is no cure for bipolar disorder; however, pharmacological treatment can substantially decrease the morbidity of acute manic episodes. To date, five medications that are commonly used for treatment of acute mania, associated with bipolar. These are Lithium, Divalproex, Olanzapine, Risperidone and Haloperidol. However, only about 60% of patients respond to any one of these medications and in addition, many patients are unable to tolerate these agents. Therefore, there was a need to develop a safer and a more tolerable drug for the treatment of acute mania associated with bipolar.

In the psychosis/schizophrenia studies, Quetiapine has established a good safety and tolerability profile. Hence, because of known and significant overlap between the symptoms of schizophrenia and acute mania, including agitation, aggression, paranoia, hallucinations, delusions, and suicidal behavior, the therapy with Quetiapine may offer efficacy with a better tolerability over the other treatments, for the treatment of acute mania associated with bipolar disorder.

2.1.2 Objectives in Treatment of Bipolar Disorder

For an agent, important attributes for in treatment of acute mania include:

- Provides clinical efficacy in the treatment of a broad range of manic symptoms.
- Improves depressive symptoms, psychotic symptoms, agitation and aggression, and functional impairment associated with acute mania.
- It is generally safe and well tolerated.

For some patients, the monotherapy with an agent might be desirable and effective. However, for many other patients, a combination therapy might be required for the proper treatment. Therefore, it is highly desirable to look into a medication with a desirable efficacy and good tolerability, when used as monotherapy or as adjunct therapy.

2.1.3 Clinical development program

The submission has designated four (**4**) clinical studies as the key studies for the evaluation of the safety and efficacy of Quetiapine in the treatment of acute mania in bipolar disorder. Two of these studies, **IL/0104** and **IL/0105**, assess its effectiveness as a monotherapy (data is submitted as the Serial No. SE1-016) and the other two studies, **IL/0099** and **IL/0100** (data is submitted as the Serial No. SE1-017), assessing its effectiveness as an adjunct to mood stabilizers (lithium or Divalproex).

All these studies are multicenter/multinational, randomized, double-blind, placebo-controlled studies:

- Study IL/0104 was conducted in the Far East (China, Indonesia, The Philippines and Taiwan) South America (Argentina and Chile) and Eastern Europe (Croatia, Estonia, Latvia, Lithuania and Poland).

- Study IL/0105 was conducted in Europe (Bulgaria, Croatia, Greece, Romania, Russia and Turkey), India and China.

- Study IL/0099 was conducted in the United States

- Study IL/0100 was conducted in Canada, Europe, India and South Africa.

The objectives, across all four studies, were to address the key treatment goals of assessing Quetiapine as monotherapy and/or adjunct therapy with respect to:

- Effectiveness in treating acute mania (primary objective).

- Effectiveness in treating depressive symptoms, psychotic symptoms of patients with psychotic symptoms at baseline, agitation and aggression, and to improve functional status.

- Safety and tolerability, across all four studies, in the treatment of acute mania.

All these four studies will be reviewed for the statistical evaluation. This review is mainly aimed as for the efficacy evaluation. The readers may consult the clinical review's review for the safety evaluation.

The detail of the design, clinical conduct and the efficacy results are given in Section 4.

2.2 DATA SOURCES

The information used for the preparation of this review consists of all NDA 20-639 documents that are installed electronically into the EDR. Those include the statistical report of the NDA and SAS data sets.

The clinical reports, relevant to this review are submitted in the following addresses:

\\cdsesub1\N20639\2002-12-30\clinstat\indication\controlled

And

\\cdsesub1\N20639\2002-12-30\summary

There has been no problem with the quality of submission and accessibility to the documents and the data.

3 STATISTICAL EVALUATION

This review is focused on the efficacy results of the drug. The readers my consult the clinical reviews for the evaluation of the safety aspect of the drug.

3.1 EVALUATION OF EFFICACY

The submission contains data in supporting the use of Seroquel as a monotherapy (Studies IL/0104 and IL/0105) and as an adjunct therapy (Studies IL/0099 and IL/0100), for the treatment of mania associated with bipolar disorder. This section is organized to present the results for monotherapy and adjunct therapy in separate subsections.

3.1.1 Seroquel as a Monotherapy

Submission contains two monotherapy studies, IL/0104 and IL/0105 that are very much similar with respect to the design, dosage, patient population, primary and secondary endpoints, etc. These common aspects will be discussed, in the next section, collectively for both studies. However, the patient disposition and efficacy results will be discussed for the individual studies.

3.1.1.1 Study Design

Both studies were designed as multicenter (multinational), double-blind, randomized, parallel-group, placebo-controlled, 12-week studies to compare the effects of Quetiapine with placebo. Each study also has an active treatment arm as well as a comparator. Haloperidol was in Study IL/0204 and Lithium in Study IL/0105.

The eligible patients were those who were hospitalized for treatment of acute mania and for manic acute manic disorder.

These two studies were conducted in sites located in the countries in Asia and Europe. Therefore, there **were no US sites** in these two monotherapy studies.

3.1.1.2 Therapy Strategy and Dosage

Quetiapine dosing was initiated at 100 mg/day on Day 1 increasing to 400 mg/day on Day 4 in increments of 100 mg/day. The Quetiapine dose could be adjusted to between 200 and 600 mg/day on Day 5, and to between 200 and 800 mg/day on Days 6 to 84, based on efficacy and/or tolerability issues.

In Study IL/0104 haloperidol dosing was initiated at 2 mg/day. The range was between 2 and 8 mg/day on Days 6 to 84, based on efficacy and/or tolerability issues.

In Study IL/0105 lithium dosing was initiated on Day 1 at a dose of 900 mg/day. Dose adjustment between Days 5 and 84 was at the discretion of the dosing investigator in order to achieve symptom control and/or minimize side effects issues.

3.1.1.3 Primary and Secondary Endpoints

For both studies the primary endpoint was change at Day 21 from baseline (Day 1) in YMRS Total score (**CT_YMRS**). There are 13 secondary endpoints. Those include: CT_YMRS at Day 84, YMRS response rate, Time to response, YMRS remission rate, Change from baseline in MADRS, etc.

At a meeting with the HFD-120 medical division, it was decided that there is no need to discuss secondary endpoints in this review.

3.1.1.4 Sponsor's Statistical Methods

The sponsor used **LOCF** to perform the analysis of covariance (**ANCOVA**) to analyze the primary and secondary efficacy variables measured by rating scales. These variables were analyzed as continuous variables. The ANCOVA used **change from baseline** as the **dependent variable**, **baseline** used as a **covariate**, **treatment** as a **fixed** effect and **center** as the **random** effect[1] in the models. Further ANCOVA was conducted for the combined data of the two studies and in order to adjust for a difference in the level of response between the two trials, the study factor was included in the model as a fixed effect and center within study was included as a random effect.

The Cochran-Mantel-Haenszel test was used for the analysis of the binary response variables.

3.1.1.5 Reviewer's Statistical Methods

As an **alternative** to the sponsor's **primary** analysis of **ANCOVA**, for both studies, this reviewer used a "**Mixed-Effects Model, Repeated Measure Approach**", denoted by **MMRM**[2] to analyze the data of primary efficacy variable YMRS total score (**T_YMRS**). The method for each patient uses all available T_YMRS measurements from baseline to the point of withdrawal

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[1] The **ANCOVA** modes used **center** as a **random** effect, but, it is not clear and this reviewer could not verify as to if the Treatment-by-Center interaction was included in the models. If the interaction is not included in the ANCOVA model, then there will be no difference for the estimation and test of hypothesis of no treatment effect, whether the center was treated as a random or as a fixed effect. The only difference will be in the interpretation of the results of test of hypothesis of **center** effect.

[2] The following technical note describes the SAS codes this reviewer used to perform MMRM:

```
Proc Mixed;
class patient treatment visit;
model CT_YMRS = B_YMRS visit  treatment treatment*visit/ddfm=satterth;
repeated visit/sub=patient type=un;
lsmeans treatment*visit/cl diff;
```

The analysis used **unstructured** covariance matrix and the results produced by the treatment*visit interaction for the last visit (endpoint) was used for the pairwise comparison of the treatments.

Further, it is known that if the missing mechanism is the "Non-Ignorable" (NI) both LOCF and MMRM results are subjected to bias. For the cases of "Missing Completely at Random" (MCAR) or "Missing at Random" (MAR), the MMRM results are robust. However, it is difficult to characterize the nature of the missing mechanism.

or completion of study. The model used change from baseline in T_YMRS (**CT_YMRS**) as the dependent variable, baseline as the covariate, treatment and visit as class variables and the Treatment-by-Visit interaction.

3.1.1.6 Demographic Configuration

A total of 302 patients were randomized in each of the two studies. Table 7 presents the demographic configuration of Studies IL/0104 1and IL/0105.

Table 7. ***(Monotherapy Studies):*** **Demographic Configuration**[+]

	IL/0104			IL/0105		
	QTP	PLA	HAL	QTP	PLA	LI
	N=101	N=100	N=98	N=107	N=95	N=98
Sex: n (%)						
Male	37 (36.6)	37 (37.0)	36 (36.7)	60 (56.1)	55 (57.9)	58 (59.2)
Female	64 (63.4)	63 (63.0)	62 (63.3)	47 (43.9)	40 (42.1)	40 (40.8)
Age (years)						
Mean (SD)	42.9 (12.92)	40.6 (12.42)	45.1 (13.42)	38.0 (12.42)	41.3 (13.70)	38.8 (13.97)
Minimum to Maximum	18 to 79	18 to 72	18 to 76	18 to 72	18 to 70	18 to 73
Age distribution: n (%)						
<18 years	0	0	0	0	0	0
18 to 39 years	39 (38.6)	43 (43.0)	32 (32.7)	57 (53.3)	45 (47.4)	56 (57.1)
40 to 64 years	57 (56.4)	55 (55.0)	56 (57.1)	47 (43.9)	45 (47.4)	36 (36.7)
≥65 years	5 (5.0)	2 (2.0)	10 (10.2)	3 (2.8)	5 (5.3)	6 (6.1)
Race: n (%)						
Caucasian	77 (76.2)	72 (72.0)	73 (74.5)	58 (54.2)	47 (49.5)	50 (51.0)
Black	0	0	0	0	0	0
Hispanic	2 (2.0)	4 (4.0)	5 (5.1)	0	0	0
Asian/Oriental	19 (18.8)	22 (22.0)	20 (20.4)	49 (45.8)	48 (50.5)	48 (49.0)
Mixed	3 (3.0)	2 (2.0)	0	0	0	0
Other	0	0	0	0	0	0

[+]This table is a cut-and-past of Table 2.7.3A-5 from the applicant's electronic Document in EDR. Numbers in (%) are the percentages.

Table 7 shows the number of patients that were qualified for the efficacy assessment, based on the Modified Intent to Treat (**MITT**) definition, which includes all randomized patients who took study medication and who had baseline and at least 1 set of post-baseline YMRS assessments. Table provides information with respect to the distributions of sex, age group and race for the two Studies and as can be seen, overall, the randomization has provided a balance with respect to these distributions across the three treatment arms, for both studies.

3.1.1.7 Analyses Results of Study IL/0104 Data

3.1.1.7.1 Patient Disposition

Table 8 presents the number of patients at each visit after randomization to their medications. As Table 8 shows, the percentage of dropouts at Day 21 are 18%, 22% and 13% for Placebo, Quetiapine and Haloperidol, respectively. These percentage rates of dropouts can be considered as moderate as compared to typical bipolar studies. However, the dropout rates are high at the magnitudes of 58%, 46% and 45% for Placebo, Quetiapine and Haloperidol, respectively.

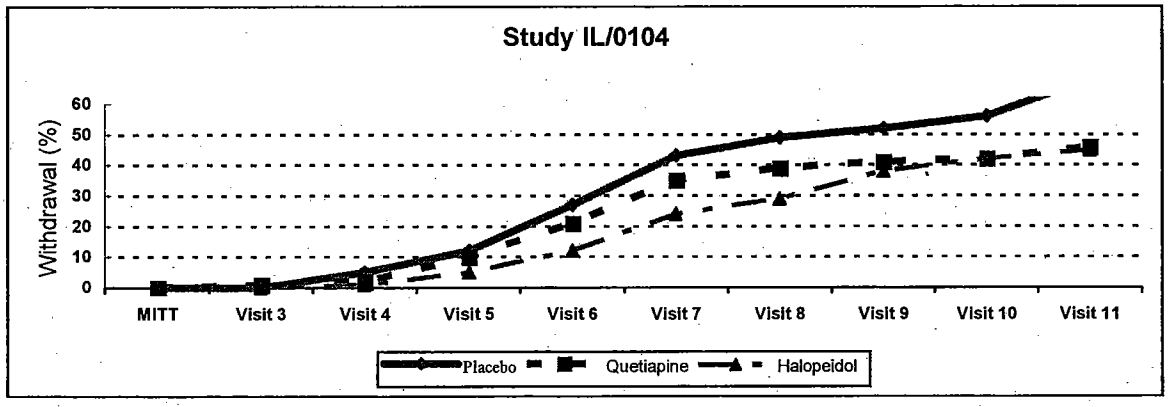
Table 8. ***(Monotherapy Study IL/0104):*** Number and Percentage of Patients Available at Each Visit[§]

Treatment	Stayed or Dropped	Patients' Visit										
		Rand	MITT	Visit 3	Visit 4	Visit 5	**Visit 6 Day 21**	Visit 7	Visit 8	Visit 9	Visit 10	**Visit 11 Day 84**
Quetiapine	Stayed (N)	102	101	100	99	91	80	66	62	60	59	55
	Stayed (%)	--	100	99	98	90	79	65	61	59	58	54
	Dropped (%)	--	0	1	2	10	21	35	39	41	42	46
Placebo	Stayed (N)	101	100	100	95	88	73	57	51	48	44	42
	Stayed (%)	--	100	100	95	88	73	57	51	48	44	42
	Dropped (%)	--	0	0	5	12	27	43	49	52	56	58
Haloperidol	Stayed (N)	99	98	98	97	93	86	74	70	61	57	54
	Stayed (%)	--	100	100	99	95	88	76	71	62	58	55
	Dropped (%)	--	0	0	1	5	12	24	29	38	42	45

§: The results are from this reviewer's analysis.

Figure 1 facilitates the visual illustration of the percent dropout at randomization and at each visit. The figure shows comparable dropouts among the arms up to visit 6 but higher percentage of placebo dropouts starting from Visit 7.

Figure 1. ***(Study IL/0104):*** Plot of Percentage of Patients Withdrew From the Study by Visit



3.1.1.7.2 Efficacy Results

3.1.1.7.2.1 Sponsor's Results

Table 9 provides the sponsor's results with respect to the primary efficacy variable of CT_YMRS and it shows that[3]:

- At Day 21 Quetiapine is statistically significantly superior to placebo (P<0.0001); Haloperidol is statistically significantly superior to placebo (P<0.0001); Haloperidol is statistically significantly superior to Quetiapine.

- At Day 84 Quetiapine is statistically significantly superior to placebo (P<0.0001); Haloperidol is statistically significantly superior to placebo (P<0.0001); however, no statistically significant difference between Quetiapine and Haloperidol.

Table 9. ***(Monotherapy Study IL/0104):*** Sponsor's Efficacy Analysis Results on CT_YMRS[$]

Day of Assessment	Attribute	Study IL/0104					
		Treatment			Comparison		
		QTP	PLA	HAL	QTP - PLA	HAL - PLA	QTP - HAL
Day 21	N (MITT)	101	100	98			
	Mean Δ	-12.29	-8.32	-15.71	-3.97	-7.39	3.42
	P-Val				**0.0096**	**<0.0001**	**SIG**
	95% CI				-6.96, -0.97	-10.40, -4.37	0.40, 6.44
Day 84	N (MITT)	101	100	98			
	Mean Δ	-17.52	-9.48	-18.92	-8.04	-9.44	1.40
	P-Val				**<0.0001**	**<0.0001**	N-SIG
	95% CI				-11.83, -4.25	-13.26, -5.62	-2.43, 5.32

$: The results are extracted from Table 30 (Day 21) and 31 (Day 84) of the sponsor's report for Study IL/0104.

3.1.1.7.2.2 Reviewer's Results

Table 10 presents the reviewer's results with respect to the primary efficacy variable of T_YMRS

Table 10. ***(Monotherapy Study IL/0104):*** Reviewer's Efficacy Analysis Results on CT_YMRS

Day of Assessment	Attribute	Study IL/0104					
		Treatment			Comparison		
		QTP	PLA	HAL	QTP - PLA	HAL - PLA	QTP – HAL
Day 21	N (MITT)	101	100	98			
	Mean Δ	-13.14	-8.80	-16.37	-4.34	-7.19	2.86
	P-Val				**0.0089**	**<0.0001**	0.0783
Day 84	N (MITT)	101	100	98			
	Mean Δ	-18.86	-10.62	-20.18	-8.92	-7.61	-1.32
	P-Val				**<0.0001**	**<0.0001**	0.4478

[3] To verify the sponsor's results, this reviewer **reanalyzed** the data according to the sponsors ANCOVA model. There were **minor** differences in the LS Means and hence the P-Values. However, the results were very close, leading to the **same** conclusions.

Table 10 shows that:

- At Day 21 Quetiapine is statistically significantly superior to placebo (P=0.0089); Haloperidol is statistically significantly superior to placebo (P<0.0001); however, there is no statistically significant difference between Quetiapine and Haloperidol.

- At Day 84 Quetiapine is statistically significantly superior to placebo (P<0.0001); Haloperidol is statistically significantly superior to placebo (P0.0001); however, there is no statistically significant difference between Quetiapine and Haloperidol.

The results in Table 9 and 10 are similar (Except for the comparison of Quetiapine with Haloperidol at Day 84) and they lead to the same conclusion of **superiority** of both **Quetiapine** and **Haloperidol** to **placebo**.

3.1.1.8 Analyses Results of Study IL\0105 Data

3.1.1.8.1 Patient Disposition

Table 11 presents the number of patients at each visit after randomization to their medications. It shows that: the percentage of dropouts at Day 21 (Visit 6) is 12%, 1% and 5% for Placebo, Quetiapine and Lithium, respectively. These percentage rates of dropouts are low compared to what has been observed in the typical bipolar studies. However, the dropout rates are much high at the end, namely day 84, at the magnitudes of 64%, 31% and 32% for Placebo, Quetiapine and Haloperidol, respectively.

Table 11. ***(Monotherapy Study IL/0105):*** Number and Percentage of Patients Available at Each Visit[§]

Treatment	Stayed or Dropped	Patients' Visit										
		Rand	MITT	Visit 3	Visit 4	Visit 5	**Visit 6 Day 21**	Visit 7	Visit 8	Visit 9	Visit 10	**Visit 11 Day 84**
Quetiapine	Stayed (N)	107	107	107	105	101	102	93	89	84	79	74
	Stayed (%)	--	100	100	98	94	95	87	83	79	74	69
	Dropped (%)	--	0	0	2	6	[redacted]	13	17	21	26	[redacted]
Placebo	Stayed (N)	99	95	94	92	88	79	64	55	43	39	35
	Stayed (%)	--	100	99	97	93	83	67	58	45	41	37
	Dropped (%)	--	0	1	3	7	[redacted]	33	42	55	59	[redacted]
Haloperidol	Stayed (N)	98	98	98	95	93	88	80	75	72	66	67
	Stayed (%)	--	100	100	97	95	90	82	77	73	67	68
	Dropped (%)	--	0	0	3	5	[redacted]	18	23	27	33	[redacted]

§: The results are from this reviewer's analysis.

Figure 2 facilitates the visual inspection of the dropout rates at randomization and at each visit.

Figure 2. ***(Study IL/0105):*** Plot of Percentage of Patients Withdrew From the Study by Visit

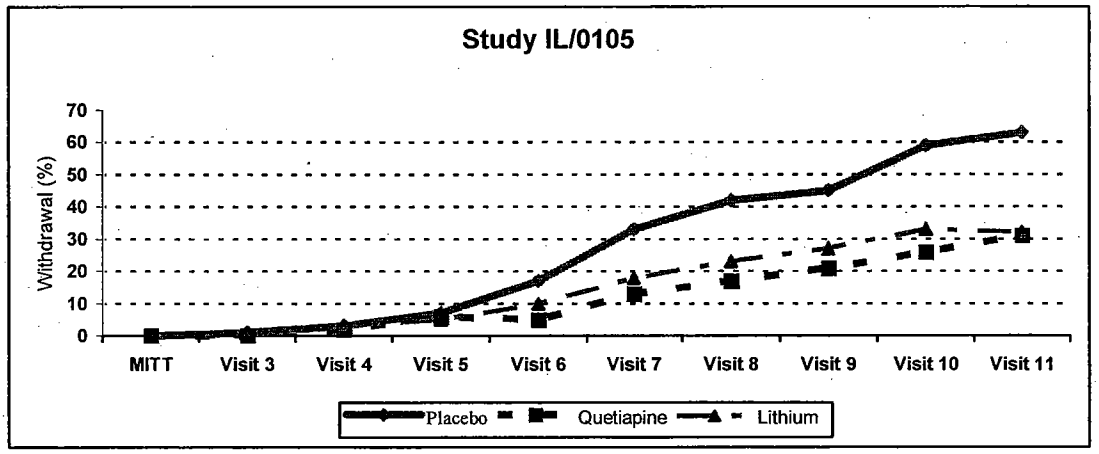


Figure 2 shows comparable dropouts among the arms up to visit 6 (Day 21). The dropout rates increases rapidly after Visit 6 with higher increasing rate for the placebo arm.

3.1.1.8.2 Efficacy Results

3.1.1.8.2.1 Sponsor's results

Table 12 provides the sponsor's results with respect to the primary efficacy variable of CT_YMRS ant it shows that (see footnote 3, page 14):

- At Day 21 Quetiapine is statistically significantly superior to placebo (P<0.0001); Lithium statistically significantly superior to placebo (P<0.0001); however, there is no statistically significantly difference between Quetiapine and Lithium.

- At Day 84 Quetiapine is statistically significantly superior to placebo (P<0.0001); Lithium is statistically significantly superior to placebo (P<0.0001); however, there is no statistically significant difference between Quetiapine and Haloperidol.

Table 12. ***(Monotherapy Study IL/0105):*** Sponsor's Efficacy Analysis Results on CT_YMRS[$]

Day of Assessment	Attribute	Study IL/0105					
		Treatment			Comparison		
		QTP	PLA	LIT	QTP -PLA	LIT -PLA	QTP – LIT
Day 21	N (MITT)	107	95	98			
	Mean Δ	-14.62	-6.71	-15.20	-7.92	-8.49	0.57
	P-Val				**<0.0001**	**<0.0001**	N-SIG
	95% CI				-10.88, -4.95	-11.49, -5.48	-2.36, 3.50
Day 84	N (MITT)	107	95	98			
	Mean Δ	-20.28	-9.00	-20.76	-11.28	-11.75	0.48
	P-Val				**<0.0001**	**<0.0001**	N-SIG
	95% CI				-14.94, -7.61	-15.47, -8.03	-3.15, 4.10

$: The results are extracted from Table 28 (Day 21) and 29 (Day 84) of the sponsor's report for Study IL/0105.

3.1.1.8.2.2 Reviewer's Results

Table 13 presents the reviewer's results with respect to the primary efficacy variable of CT_YMRS.

Table 13. ***(Monotherapy Study IL/0105):*** Reviewer's Efficacy Analysis Results on CT_YMRS

Day of Assessment	Attribute	Study IL/0105					
		Treatment			Comparison		
		QTP	PLA	LIT	QTP - PLA	LIT - PLA	QTP – LIT
Day 21	N (MITT)	107	95	98			
	Mean Δ	-16.07	-8.61	-17.29	-7.56	-9.00	1.44
	P-Val				**<0.0001**	**<0.0001**	0.3979
Day 84	N (MITT)	107	95	98			
	Mean Δ	-17.37	-12.90	-18.78	-4.31	-5.91	1.59
	P-Val				**0.0043**	**0.0002**	0.2344

Table 13 shows that:

- At Day 21 Quetiapine is statistically significantly superior to placebo ($P < 0.0001$); Lithium is statistically significantly superior to placebo ($P < 0.0001$); however, there is no statistically significant difference between Quetiapine and Lithium ($P=0.3979$).

- At Day 42 Quetiapine is statistically significantly superior to placebo ($P = 0.0043$); Haloperidol is statistically significantly superior to placebo ($P =0.0002$); however, there is no statistically significant difference between Quetiapine and Lithium.

3.1.1.9 Conclusion on Monotherapy Studies

The results presented in Table 12 and 13 are very much similar and lead to the same conclusion. Therefore, both the sponsor's and the reviewer's analysis confirm the conclusion of **superiority** of both **Quetiapine** and **Lithium** to placebo, but, no statistically significantly different between **Quetiapine** and **Lithium.**

3.1.2 Seroquel as an Adjunct Therapy

Similar to the case of monotherapy, the two adjunct therapy studies IL/0099 and IL/0100 are very much similar with respect to the design, dosage, patient population, primary and secondary endpoints, etc. We discussed these aspects in the following sub-sections, collectively for both studies. However, the analysis results of patient disposition and efficacy will be discussed, individually, for each study.

3.1.2.1 Study Design

Both studies designed as multicenter, double-blind, randomized, parallel-group, placebo-controlled studies. As an adjunct, the Quetiapine was added to the mood stabilizer drugs Lithium or Divalproex. For the placebo patients, the placebo was added to these two stabilizers.

The duration of randomized treatment was 21 days in Study IL/0099 and 42 days in Study IL/0100. Study IL/0099 was conducted in the United States and Study IL/0100 was conducted in Canada, Europe, India and South Africa.

The eligible patients were those who were hospitalized for treatment of acute mania and for manic acute manic disorder.

3.1.2.2 Therapy Strategy and Dosage

Quetiapine dosing was initiated at 100 mg/day on Day 1 increasing to 400 mg/day on Day 4 in increments of 100 mg/day. The Quetiapine dose could be adjusted to between 200 and 600 mg/day on Day 5, and to between 200 and 800 mg/day on Days 6 to 84, based on efficacy and/or tolerability issues.

Lithium and Divalproex were to be administered at dose regimens determined by the investigator to achieve trough serum lithium concentrations of 0.7 mEq/L to 1.0 mEq/L and trough serum Divalproex concentrations of 50 mg/mL to 100 mg/mL.

3.1.2.3 Primary and Secondary Endpoints

The primary and secondary endpoints are the same as those discussed for the monotherapy studies. However, for the readers' convenience we discuss it here as well. For both studies the primary endpoint was change at Day 21 from baseline (Day 1) in YMRS Total score (**CT_YMRS**). There secondary endpoints include YMRS response rate, Time to response, YMRS remission rate, Change from baseline in MADRS, etc. CT_YMRS at Day 42 was also a secondary endpoint.

At a meeting with the Clinical Reviewing team of the Division Neurological Drug Products (HFD-120), it was decided that there is no need to discuss secondary endpoints in this review.

3.1.2.4 Sponsor's Statistical Methods

Similar to the monotherapy cases, here also, for both studies, the sponsor analysis is **ANCOVA,** using LOCF to analyze the primary and secondary efficacy variables. The model used change from baseline as dependent variable, baseline a covariate, treatment as fixed effect and center as random effect (see Footnote 1, page 12).

The Cochran-Mantel-Haenszel test was used for the analysis of the binary response variables.

3.1.2.5 Reviewer's Statistical Methods

As described for the monotherapy case, as a **secondary** analysis, for both studies the reviewer's analysis consists of Mixed-Effects Model, Repeated Measure Approach" **(MMRM)** to analyze the data of primary efficacy variable T_YMRS. The model used change from baseline in T_YMRS (**CT_YMRS**) as the dependent variable, baseline as the covariate, treatment and visit as class variables and the Treatment-by-Visit interaction (see Footnote 2, page 12).

Table 14. *(Adjunct Therapy Studies):* **Demographic Configuration**[+]

	IL/0099			IL/0100		
	QTP + LI/DVP	PLA + LI/DVP	Total	QTP + LI/DVP	PLA + LI/DVP	Total
	N=81	N=89	N=170	N=104	N=96	N=200
Sex: n (%)						
Male	49 (60.5)	47 (52.8)	96 (56.5)	51 (49.0)	49 (51.0)	100 (50.0)
Female	32 (39.5)	42 (47.2)	74 (43.5)	53 (51.0)	47 (49.0)	100 (50.0)
Age (years)						
Mean (SD)	39.6 (10.08)	41.3 (11.95)	40.5 (11.10)	38.8 (13.26)	40.1 (11.64)	39.5 (12.49)
Min to Max	18 to 61	18 to 70	18 to 70	20 to 70	19 to 70	19 to 70
Age distribution: n (%)						
< 18	0	0	0	0	0	0
18-39	37 (45.7)	42 (47.2)	79 (46.5)	57 (54.8)	46 (47.9)	103 (51.5)
40-64	44 (54.3)	42 (47.2)	86 (50.6)	43 (41.3)	48 (50.0)	91 (45.5)
≥65	0	5 (5.6)	5 (2.9)	4 (3.8)	2 (2.1)	6 (3.0)
Race: n (%)						
Caucasian	54 (66.7)	67 (75.3)	121 (71.2)	76 (73.1)	71 (74.0)	147 (73.5)
Black	17 (21.0)	15 (16.9)	32 (18.8)	2 (1.9)	1 (1.0)	3 (1.5)
Hispanic	6 (7.4)	5 (5.6)	11 (6.5)	1 (1.0)	0	1 (0.5)
Asian/Oriental	1 (1.2)	1 (1.1)	2 (1.2)	5 (4.8)	4 (4.2)	9 (4.5)
Mixed	1 (1.2)	1 (1.1)	2 (1.2)	3 (2.9)	5 (5.2)	8 (4.0)
Other[5]	2 (2.5)	0	2 (1.2)	17 (16.3)	15 (15.6)	32 (16.0)

+: This table is a cut-and-past of Table 2.7.3B-5 from the applicant's electronic Document in EDR.

Numbers in (%) are the percentages.

3.1.2.6 Demographic Configuration

Table 14 presents the demographic configuration of adjunct therapy Studies and it shows that:

A total of 191 and 209 patients were randomized in studies IL/009 and IL/0100, respectively. Table 14 shows that then number of patients qualified for the efficacy assessment, based on the Modified Intent to Treat (**MITT**) was 170 and 200 for the studies IL/009 and IL/0100, respectively. Table provides information with respect to the distributions of sex, age group and race for the two studies and as can be seen, overall, relatively, the randomization has provided a balance with respect to these distributions across the two treatment arms, for both studies.

3.1.2.7 Analyses Results of Study IL/0099 Data

Study IL/0099 was a 21-Day study and the results are presented below.

3.1.2.7.1 Patient Disposition

Table 15 presents the number of patients at each visit after randomization to their medications.

Table 15. ***(Adjunct Therapy Study IL/0099):*** Number and Percentage of Patients Available at Each Visit[§]

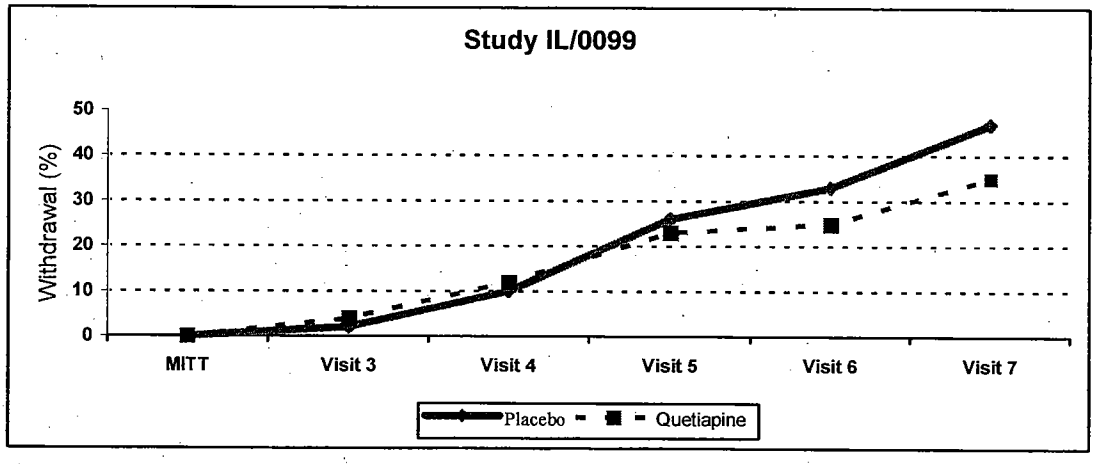
Treatment	Stayed or Dropped	Visit						
		Rand	MITT	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Quetiapine	Stayed (N)	91	81	78	71	62	61	53
	Stayed (%)	--	100	96	88	77	75	65
	Dropped (%)	0	0	4	12	23	25	[redacted]
Placebo	Stayed (N)	100	89	87	80	66	60	47
	Stayed (%)	--	100	98	90	74	67	53
	Dropped (%)	0	0	2	10	26	33	[redacted]

§: The results are from this reviewer's analysis.

Table 15 shows that, the percentage of dropouts at Day 21 (Visit 7) is 47% for placebo and 35% for Quetiapine. These percentage rates of dropouts are high as compared to those seen for the monotherapy studies.

Figure 3 facilitates a visual inspection for the dropout rates throughout the trial.

Figure 3. ***(Study IL/0099):*** Plot of Percentage of Patients Withdrew From the Study by Visit



3.1.2.7.2 Efficacy Results

3.1.2.7.2.1 Sponsor's Results

Table 16 provides the sponsor's results with respect to the primary efficacy variable of T_YMRS (see Footnote 3, Page 14).

Table 16. ***(Adjunct Therapy Study IL/0099):*** Sponsor's Efficacy Analysis Results on CT_YMRS[$]

Day of Assessment	Attribute	Study IL/0099		
		Treatment		Comparison
		QTP[†]	PLA[†]	QTP - PLA
Day 21	N (MITT)	81	89	
	Mean Δ	-13.76	-9.93	-3.82
	P-Val			0.0209
	95% CI			-7.06, -0.59

†: The Quetiapine and placebo treatments were added as adjunct to Lithium or Divalproex.
$: The results are extracted from Table 31 of the sponsor's report for Study IL/0099.

Table 16 shows that, at Day 21 Quetiapine is statistically significantly superior to placebo P=0.0209).

3.1.2.7.2.2 Reviewer's Results

Table 17 provides the sponsor's results with respect to the primary efficacy variable of T_YMRS.

Table 17. ***(Adjunct Therapy Study IL/0099):*** Reviewer's Efficacy Analysis Results on CT_YMRS[$]

Day of Assessment	Attribute	Study IL/0099		
		Treatment (Raw Means)		Comparison LS Means
		QTP[†]	PLA[†]	QTP - PLA
Day 21	N (MITT)	81	89	
	Mean Δ	-12.42	-9.03	-5.64
	P-Val			0.0025

†: The Quetiapine and placebo treatments were added as adjunct to Lithium or Divalproex.

As Table 17 shows, the statistical reviewer's results confirms the sponsor's results, indicating that Quetiapine is statistically significantly superior to placebo (P=0.0025).

The results from this study shows that, although Quetiapine is effective in treatment of bipolar, however, the strength of its effect is not as strong as when it is used as a monotherapy, as shown in the monotherapy studies (where P< 0.0001).

3.1.2.8 Analyses Results of Study IL/0100 Data

Study IL/0100 was a 42-Day trial. However, Day 21 was the primary endpoint. The results are presented below.

3.1.2.8.1 Patient Disposition

Table 18 presents the number of patients at each visit after randomization at it shows that shows, the percentage of dropouts at Day 21 (Visit 6) is 13% and 23% for Quetiapine and placebo, respectively. These dropout rates are moderate compared to what has been observed in the

typical bipolar studies. The dropout rates at Day 42 (Visit 10) are 33% and 40% for Quetiapine and placebo, respectively.

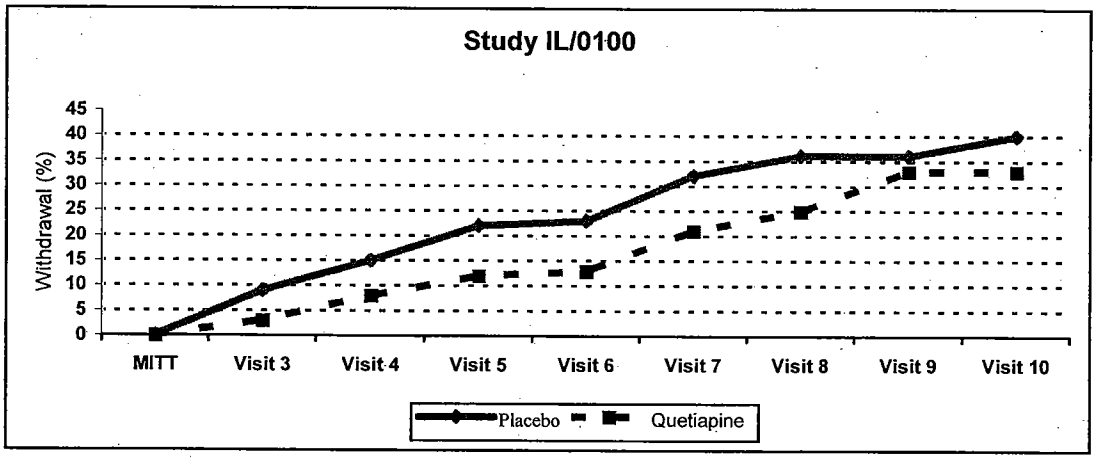
Table 18. ***(Adjunct Therapy Study IL/0100):*** Number and Percentage of Patients Available at Each Visit[§]

Treatment	Stayed or Dropped	Patients' Visit									
		Rand	MITT	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Quetiapine	Stayed (N)	106	106	103	97	93	92	84	79	71	71
	Stayed (%)	--	100	97	92	88	87	79	75	67	67
	Dropped (%)	--	0	3	8	12	[redacted]	21	25	33	[redacted]
Placebo	Stayed (N)	103	103	94	88	80	78	70	66	66	62
	Stayed (%)	--	100	91	85	78	77	68	64	64	60
	Dropped (%)	--	0	9	15	22	[redacted]	32	36	36	[redacted]

§: The results are from this reviewer's analysis.

Figure 4 provides a tool for the visual inspection of the dropout rates at randomization and at each visit. The figure shows higher dropout rate for placebo as compared to Quetiapine, consistently, immediately after randomization (MITT).

Figure 4. ***(Study IL/0100):*** Plot of Percentage of Patients Withdrew From the Study by Visit



3.1.2.8.2 Efficacy Results

3.1.2.8.2.1 Sponsor's Results

Table 19 provides the sponsor's results with respect to the primary efficacy variable of T_YMRS (see Footnote 3, Page 14). Table 19 shows that at both Day 21 and Day 42, the results failed to demonstrate a statistical significant difference between Quetiapine and placebo. The P-Value at Day 21 was 0.2809.

Table 19. ***(Adjunct Therapy Study IL/0100):*** Sponsor's Efficacy Analysis Results on CT_YMRS[$]

Day of Assessment	Attribute	Study IL/0100		
		Treatment		Comparison
		QTP[†]	PLA[†]	QTP - PLA
Day 21	N (MITT)	104	96	
	Mean Δ	-15.19	-13.22	-1.97
	P-Val			0.2809
	95% CI			-5.6, 1.6
Day 42	N (MITT)	104	96	
	Mean Δ	-17.10	-14.27	-2.83
	P-Val			N-SIG
	95% CI			-6.9, 1.2

†: The Quetiapine and placebo treatments were added as adjunct to Lithium or Divalproex.
$: The results are extracted from Table 65 for both Days 21 and 42 of the sponsor's report for Study IL/0100.

3.1.2.8.3 Reviewer Analysis

Table 20 contains this reviewer's results and it confirms the results of the sponsor that, at both Day 21 and Day 42, the results failed to demonstrate a statistical significant difference between Quetiapine and placebo. The P-Values at Day 21 and 42 are 0.6244 and 0.5079, respectively.

Table 20. ***(Adjunct Therapy Study IL/0100):*** Reviewer's Efficacy Analysis Results on CT_YMRS

Day of Assessment	Attribute	Study IL/0100		
		Treatment		Comparison
		QTP[†]	PLA[†]	QTP - PLA
Day 21	N (MITT)	104	96	
	Mean Δ	-12.35	-11.30	-0.8783
	P-Val			0.6244
Day 42	N (MITT)	104	96	
	Mean Δ	-17.10	-14.27	-1.30
	P-Val			0.5079

†: The Quetiapine and placebo treatments were added as adjunct to Lithium or Divalproex.

3.1.2.9 Conclusion on Adjunct Therapy Studies

The results presented in Tables 16 and 17 show that, in Study IL/0099 (a US Study), there was a statistically significant difference between Quetiapine and placebo. However, for Study IL/0100 (conducted in Canada, Europe, India and South Africa), results in Tables 19 and 20 show that there is no statistical significant difference between Quetiapine and placebo, but the numerical results are slightly in favor of Quetiapine.

3.2 EVALUATION OF SAFETY

Safety will not be discussed in this review. The readers may consult the clinical reviewer's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup findings, presented below, are concluded from the analysis performed by this reviewer. The analyses are limited to those for subgroups Gender, Race and the Age group. Because Study IL/0104, in adjunct therapy, did not demonstrate the efficacy of Quetiapine as compared to placebo, therefore, subgroup analysis was not performed for this study.

Since for each study as a whole, the results of the sponsor's analysis, using LOCF and ANCOVA, and this reviewer's analysis using MMRM were leaded to the same conclusion, therefore, the subgroup analysis performed using LOCF and ANCOVA. The analysis will use CY_YMRS. Further, for the Studies IL/0104 and IL/0105, only the data of patients randomized to placebo and Quetiapine was used in the analysis.

Table 21, extracted from Table 7 and 14, presents a summary of the race distribution for Studies IL/0104, IL/0105 and IL/0099. Table 21 shows that, overall, the majority of patients are Caucasians (49.5% to 76.2%). The next largest race population is "Asians/Orientals" in Studies IL/0104 and IL/0105 (18.2% to 50.5%) and then the population of Blacks in Study IL/0099 (16.9% to 21.0%). Since there was low percentage of patients for the other races, therefore, two categories of "Caucasians" and "Others", which includes all races other than Caucasians, were used in the analysis.

Table 21. ***(Studies IL/0104, IL/0105 and IL/0099):*** Race Distribution by Treatment Group [$]

Race Group	Study IL/0104		Study IL/0105		Study IL/0099	
	Quetiapine	Placebo	Quetiapine	Placebo	Quetiapine	Placebo
Caucasian	76.2%	72.0%	54.2%	49.5%	66.7%	75.3%
Asian/Oriental	18.2%	22.0%	45.8%	50.5%	1.2%	1.1%
Black	0.0%	0.0%	0.0%	0.0%	21.0%	16.9%
Others	5.0%	6.0%	0.0%	0.0%	11.1%	6.7%

$: Contents are from the reviewer's analysis

With respect to the age groups, as Tables 7 and 14 show, there are not many patients at or over 65 years and there are not any patients below the age of 18 year. Therefore, in consistency with the sponsor's categorization in Tables 7 and 14, the two age categories of: <40 and ≥40 will be considered in the analysis.

4.1 GENDER, RACE AND AGE

Table 22, 23, and 24 present the results of subgroup analysis with respects to the Gender, Race and Age groups. Tables present the Least Square Means of CT_YMRS, resulted from ANCOV. Tables also give P-Values for the comparison of Quetiapine vs. placebo for each subgroup as well as, within each treatment, the P-Values for the comparisons of subclasses in each subgroup. For example, P-Value for comparing males vs. Females in Quetiapine, which P=0.2875 in Table 22.

*Note: Because the **randomization** was not **stratified** by the subgroups and because the studies were not powered for the subgroup analysis, the readers should use **extra caution** in interpretation of the P-Values given in Tables 22, 23 and 24.*

All the efficacy discussions in the following subsections are with respect to the Least Square Means of CT_YMRS. To thorough, some P-values from the Tables 22, 23 and 24 will be quoted, but, the readers should take those casually, as denoted above.

4.1.1 Monotherapy Studies

Table 22 presents the subgroup for Study IL/0104. As Table 22 shows, for all subgroups and for all subclasses within each subgroup (e.g. Male and Female within Gender), these numerical results on CT_YMRS are in the direction of favoring Quetiapine over placebo. These comparisons provided small P-Values of 0.0135, 0.0365 and 0.0285 for females, other races and the age of greater than 40 years.

For the Quetiapine treatment, the numerical results on CT_YMRS, show larger treatment effect, however not statistically significant, has been demonstrated for females as compared to males, other races as compared to Caucasians and for the age class of younger than 40 years as compared to 40 years of age.

Table 22. ***(Study IL/0104):*** Subgroup Analysis for the Gender, Race and Age Categories [$]

		Study IL/0104				
		Quetiapine		Placebo		P-Value QTP vs. PLA
		n (%)	CT_YMRS LS Mean	n (%)	CT_YMRS LS Mean	
Gender	Total	101		100		
	Male	37 (37)	-11.4	37 (37)	-9.0	0.3994
	Female	64 (63)	-14.1	63 (63)	-8.7	**0.0135**
	P-Val: Male vs. Female		0.2875		0.9012	
Race	Total	101		100		
	Caucasian	77 (76)	-12.5	72 (72)	-8.4	**0.0365**
	Others	24 (24)	-14.9	28 (28)	-12.1	0.1468
	P-Value: Caucasian vs. Others		0.3871		0.5208	
Age	N (%)	101		100		
	Age < 40 Years	39 (39)	-13.6	43 (43)	-10.1	0.1907
	Age ≥ 40 Years	62 (62)	-12.8	57 (57)	-7.9	**0.0285**
	P-Value: <40 Years vs. ≥40 Years		0.7261		0.3569	

$: Contents are from the reviewer's analysis

Table 23 presents the subgroup analysis results for Study IL/0105. Similar results as those in Table 22, even more profoundly, have been demonstrated for Study IL/0105. Namely, for all subgroups and for all subclasses within each subgroup, the numerical results on CT_YMRS are in the direction of favoring Quetiapine over placebo. The differences have also shown to be statistically significant.

For the Quetiapine treatment, the numerical results on CT_YMRS, show larger treatment effect, however not statistically significant, has been demonstrated for males as compared to females, other races as compared to Caucasians and for the age class of younger than 40 years as compared to 40 years of age.

Table 23. ***(Study IL/0105):*** Subgroup Analysis for the Gender, Race and Age Categories [$]

		Study IL/0105				
		QTP		PLA		P-Value
		n (%)	CT_YMRS LS Mean	n (%)	CT_YMRS LS Mean	QTP vs. PLA
Gender	Total	107		95		
	Male	60	-17.0	55	-11.3	0.0122
	Female	47	-15.4	40	-4.3	**<0.0001**
	P-Val: Male vs. Female		0.4983		**0.0058**	
Race	Total	107		95		
	Caucasian	58	-14.5	47	-3.5	**<0.0001**
	Others	40	-18.5	48	-13.1	**0.0251**
	P-Value: Caucasian vs. Others		0.0817		**<0.0001**	
Age	N (%)	107		95		
	Age < 40 Years	57	-17.2	45	-9.1	**0.0011**
	Age ≥ 40 Years	50	-15.3	50	-7.6	**0.0018**
	P-Value: <40 Years vs. ≥40 Years		0.4265		0.5694	

$: Contents are from the reviewer's analysis

4.1.2 Adjunct Therapy Study IL/0099

Table 24 gives the results of subgroup analysis for Study IL/009.

Table 24. ***(Study IL/0099):*** Subgroup Analysis for the Gender, Race and Age Categories [$]

		Study IL/0104				
		QTP		PLA		P-Value
		n (%)	CT_YMRS LS Mean	n (%)	CT_YMRS LS Mean	QTP vs. PLA
Gender	Total	86		95		
	Male	51	-11.9	51	-7.7	**0.0422**
	Female	35	-11.4	44	-11.4	0.9882
	P-Val: Male vs. Female		0.8174		0.0898	
Race	Total	86		95		
	Caucasian	57	-12.9	72	-10.2	0.1469
	Others	29	-9.4	23	-6.9	0.3972
	P-Value: Caucasian vs. Others		0.1382		0.1877	
Age	N (%)	86		95		
	Age < 40 Years	39	-11.3	44	-8.8	0.3156
	Age ≥ 40 Years	47	-12.1	51	-9.9	0.2847
	P-Value: <40 Years vs. ≥40 Years		0.7220		0.5976	

$: Contents are from the reviewer's analysis

Results in Table 24 are similar to those presented in Table 23. Namely, the numerical results are profoundly in favor of Quetiapine as compared to placebo in reducing T_YMRS from baseline. This is the case for all subgroups and for all subclasses within each subgroup. These comparisons provided small P-Values of 0.0422 for males.

For the Quetiapine treatment, the numerical results show a slightly, however not statistically significant, greater effect for the Caucasians as compared to the other races.

4.1.3 Conclusion on Subgroup Analysis

Overall, for the monotherapy and adjunct therapy studies, the numerical results of subgroup analyses on CT_YMRS for gender, race and age show that for all subclasses within each subgroup (e.g. Male and/or Female within Gender), Quetiapine is more effective than placebo in treatment of bipolar patients.

The comparison of subclasses (e.g. Males vs. Females) within subgroups did not consistently produce the same results across the subgroups. Therefore, such analyses should be disregarded.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

This review will not consider other special subgroup analysis.

5 SUMMARY AND CONCLUSIONS

This NDA supplement contains two monotherapy studies (IL/0104 & IL/0105) and two adjunct therapy studies (IL/0099) & IL/0100) on Seroquel (generic Name: **Quetiapine**) for the treatment of acute maniac for patients with bipolar disorder. These four studies are multicenter/multinational (except for IL/000 which is a US study), randomized, double-blind, placebo-controlled studies:

Quetiapine was registered in the United Kingdom in July 1997, followed by the FDA in September 1997, for the treatment of psychosis/schizophrenia. Although to date there is no cure for bipolar disorder, however, because of significant overlap between the symptoms of schizophrenia and acute mania, and because Quetiapine has established a good safety record, therefore, there was a need to study Quetiapine for treatment of bipolar.

As has been discussed, in detail, in previous sections, the primary efficacy variable for the four Quetiapine studies was change from baseline to day 21 on Total YMRS scores (CT_YMRS). However, as a secondary variable, CT_YMRS was evaluated at Day 84 in Studies IL/0104 and IL/0105 and at Day 42 in Study IL/0100. As a result of a consultation with the clinical reviewer team in the Division of Neurological Drug Products (HFD-120), there was no need to include the evaluation of secondary variables in this review.

A substantial evidence of efficacy for Quetiapine was provided by Studies IL/0104, IL/0105 and IL/0099.

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

5.1.1 Statistical Issues

It is known that for the trials with large number of dropouts/missing values, an issue could be the potential bias in the results, due to inappropriate use of statistical analysis to handle the missing values. For a given study and a given analysis, there is no way to assess the bias or the extent; it depends on the type of analysis as well as the nature of the discontinuation. At any rate, simulation results show some methods are more subjected to produce bias than the others. Concerning the studies reviewed above, the duration for the primary endpoint is only 21 days and, for three of these studies moderate dropout rates were observed. As Tables 8, 11, 18 show (see Figures 1-3), the dropouts rates are in the rages of 12% to 27%, 5% to 17% and 18% to 19% for the Studies IL/0104, IL/0105 and IL/0100, respectively. However, for the as Table 15 shows, for US Study IL/0099, dropouts are in the rage of 35% to 57%, which is considered as being high. This can be an issue for the efficacy assessment of this study, specifically relative to ANCOVA using LOCF procedure. However, the sponsor's ANCOVA and this reviewer's MMRM, virtually, produced **similar** results. So, the results are **robust** against the use of the two methodologies.

5.1.2 Integrated Efficacy Results

The efficacy conclusion, in this review, is based on the sponsor's ANCOVA, the **primary analysis**, results. The reviewer's MMRM analysis results are used as **supportive**, analysis.

5.1.2.1 Monotherapy

The following table provides a summary of the sponsor's as well as this reviewer's analysis results on CT-YMRS for the monotherapy studies. The information is extracted from Tables 9, 10, 12 and 13.

Table 25. (Monotherapy Studies): Integrated Summary of Efficacy Results on CT_YMRS

Study	Sponsor's Results Extracted from Tables 9 & 10			Reviewer's Results Extracted from Tables 11 & 12		
	Quetiapine CT_YMRS Mean	Placebo CT_YMRS Mean	QTP – PLA P-Value	Quetiapine CT_YMRS Mean	Placebo	QTP – PLA P-Value
Study IL/0104	-12.3	-8.3	**0.0096**	-16.07	-8.6	**<0.0001**
Study IL/0105	-14.6	-6.7	**<0.0001**	-16.1	-8.6	**<0.0001**

Clearly, from both the sponsor's and this reviewer's analysis, the results of both studies show that Quetiapine is highly statistically significantly superior to placebo in treatment of acute mania associated with bipolar.

5.1.2.2 Adjunct Therapy

The following table provides a summary of the sponsor's and this reviewer's analysis results on CT-YMRS for the adjunct therapy studies. The information is extracted from Tables 16, 17, 19 and 20.

Table 26. (Adjunct Therapy Studies): Integrated Summary of Efficacy Results on CT_YMRS

Study	Sponsor's Results Extracted from Tables 9 & 10			Reviewer's Results Extracted from Tables 11 & 12		
	Quetiapine CT_YMRS Mean	Placebo CT_YMRS Mean	QTP – PLA P-Value	Quetiapine CT_YMRS Mean	Placebo	QTP – PLA P-Value
Study IL/0099	-13.7	-9.9	**0.0209**	-12.4	-9.0	**0.0025**
Study IL/0100	-15.2	-13.2	0.2809	-12.4	-11.3	0.6244

The results show, for Study IL/0099, both the sponsor's and this reviewer's analysis, have indicated statistically significant superiority of Quetiapine over placebo. However, results for Study IL/0100, although numerically slightly in favor of Quetiapine, but, failed to provide a statistically significant support for efficacy of Quetiapine.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The results of the **primary** analysis, performed by the sponsor, and the **alternative** analysis, performed by this reviewer, are very similar and lead to the same conclusion. Overall, the results from the two placebo controlled monotherapy studies IL/00104 and IL/0105 and the adjunct therapy Study IL/0099 have provided sufficient statistical support for the superiority of Quetiapine over placebo in treatment of patients with acute mania associated with bipolar disorder, as a monotherapy as well as an adjunct therapy. Although, the adjunct therapy IL/0100 failed to provide statistically significant results in favor if Quetiapine, the numerical results are in favor of Quetiapine over placebo.

NOTE: *The efficacy conclusion, in this review, is based on the sponsor's ANCOVA, the* ***primary analysis****, results. The reviewer's MMRM analysis results areused as* ***supportive*** *analysis. The supportive analysis confirms the primary analysis.*

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APPLICATION NUMBER:

NDA 20-639/S-016 & S-017

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20639 SE1-016/017
Generic Name:	Quetiapine
Brand Name:	Seroquel®
Sponsor:	AstraZeneca
Proposed Indication:	Treatment of acute manic episodes associated with bipolar disorder, as either monotherapy or adjunct therapy to mood stabilizers
OND Clinical Division:	Division of Neuropharmacological Drug Products (HFD-120)
OCPB Division:	Division of Pharmaceutical Evaluation 1 (HFD-860)
Submission Type:	Efficacy supplement
Submission Dates:	12/30/02, 1/16/03, 3/24/03
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

Executive Summary

Synopsis: The sponsor submitted an efficacy supplement seeking approval for the use of Seroquel as monotherapy and adjunct therapy to mood stabilizers in the treatment of acute manic episodes associated with bipolar disorder. Seroquel is currently approved for the treatment of schizophrenia.

Bipolar disorder is a complex mental illness characterized by debilitating mood swings from intense euphoria to depression. There is significant overlap between the symptoms of schizophrenia and acute mania, including agitation, aggression, paranoia, hallucinations, delusions, and suicidal behavior. For this reason, antipsychotic medications have been used to treat acute mania. The sponsor stated that currently, the first line of treatment for severe manic episodes in bipolar disorder is the initiation of a mood stabilizer plus an antipsychotic. For less ill patients, monotherapy with a mood stabilizer or an antipsychotic can be sufficient. Presently lithium, divalproex and the atypical antipsychotics olanzapine and risperidone, are commonly used for the treatment of acute mania associated with bipolar disorder. The sponsor states that quetiapine may offer efficacy with better tolerability over existing antipsychotics used for acute mania.

Quetiapine is a dibenzothiazepine derivative which interacts with a broad range of neurotransmitter receptors including serotonin (5HT2), dopamine and adrenergic receptors. It is the combination of receptor antagonism with a higher selectivity for brain serotonin relative to dopamine D2 receptors which is believed to contribute to its psychotropic activity.

The quetiapine clinical development program consisted of studies to assess the safety and effectiveness of quetiapine in the monotherapy setting and studies to assess the safety and effectiveness of quetiapine as an adjunct to mood stabilizer (Lithium and valproic acid). In the clinical efficacy and safety studies, quetiapine doses were titrated from 100 mg/day on day 1 to 400 mg/day on day 4 with dose adjustments thereafter to a maximum of 800 mg/day. The maximum recommended safe dose for treatment of schizophrenia is 800 mg/day. The sponsor was requested to conduct a study that evaluated the potential interaction between valproic acid and quetiapine. The results of that study (5077IL/0120) are included in this SNDA. A study

evaluating the potential interaction between lithium and quetiapine was provided in the original application (NDA 20639) and is cross-reference in this efficacy supplement.

A comparison of pharmacokinetic parameters for quetiapine in the presence and absence of divalproex sodium indicated that there was no significant change in the extent of exposure (AUCss) of quetiapine when coadministered with Divalproex. However, Cmax increased by 17% and the 90% CI was not contained within the recommended 80 to 125% confidence limits. The increase in Cmax may not be clinically relevant.

The maximum concentration (Cmax) and extent of exposure (AUCss) of total and free valproic acid when divalproex was administered with quetiapine were not significantly different compared to when divalproex was administered alone. The 90% CI for log transformed AUC and Cmax were contained within the recommended 80 to 125% confidence limits.

The results from the pharmacokinetic study investigating the potential for a drug interaction between divalproex sodium and quetiapine fumarate demonstrated that clinically relevant interaction is not expected when the two drugs are co-administered. The co-administration of quetiapine with divalproex was reported to be well tolerated and no new safety concerns were reported by the sponsor. The results from a previous study submitted with the original application for Seroquel (NDA 20-639) indicated that the pharmacokinetics of lithium were not altered when coadministered with quetiapine.

Recommendations: Based on the data submitted to the Human Pharmacokinetics and Bioavailability section of NDA 20-639 SE1-016/017 to fulfill section 320 and 201.5 of 21CFR, the information on the drug interactions between quetiapine and divalproex is acceptable.

Labelling Recommendations

The following proposals by the sponsor with the following additions (double underlined) are acceptable and recommended to be included in the drug interaction section of the Seroquel label

The Effect of Other Drugs on Quetiapine

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.

Effect of Quetiapine on Other Drugs

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.

Kofi A. Kumi, Ph.D._____

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

CC: NDA 20-639 SE1-016/017, HFD-120, HFD-860 (Mehta, Sahajwalla, Baweja, Kumi), CDR (Biopharm.)

Table of Content

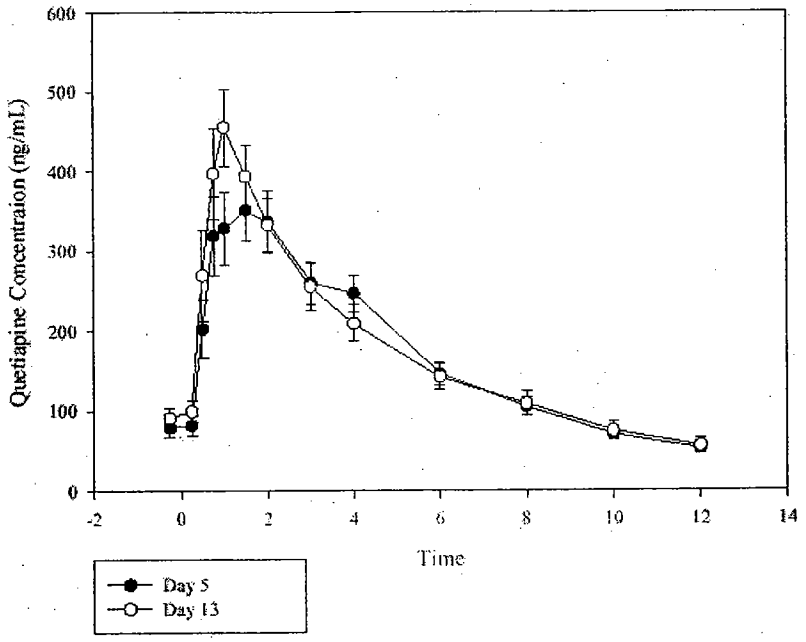
Is there clinically relevant pharmacokinetic interaction between quetiapine and valproic acid?

A comparison of the pharmacokinetic parameters for quetiapine in the presence and absence of divalproex sodium indicated that there was no significant change in the extent of exposure (AUCss) of quetiapine when coadministered with divalproex. However, Cmax increased by 17% and the 90% CI around the mean ratio fell outside the recommended 80 to 125% confidence limits. The increase in Cmax may not be clinically relevant since quetiapine is reported to have a wide therapeutic window.
The concentration of total and free valproic acid decreased by about 11% and 12%, respectively when divalproex was administered with quetiapine compared to when divalproex was administered alone. However, the 90% CI around the mean ratio was contained within the 80 to 125% recommended confidence limits. The decrease is not expected to be clinically relevant.

The study to evaluate the interaction between quetiapine and valproic acid was a multi-center, open-label, parallel, two-cohort trial. Nineteen patients with schizophrenic/schizoaffective disorders (Cohort A) and 15 patients (Cohort B) with bipolar disorder and schizoaffective disorder were exposed to quetiapine and divalproex. For Cohort A patients, quetiapine fumarate was titrated to a target dose 150 mg bid over a 5- day period. From Day 6 through Day 8, the dose of divalproex sodium was initiated and titrated to a daily dose of 500 mg bid. The patients remained at these doses of quetiapine fumarate (150 mg bid) and divalproex sodium (500 mg bid) from Day 8 through Day 13. From Day 14 to Day 17, the doses of quetiapine and of divalproex were titrated to no divalproex and to the patients' pre-study dosing regimens of quetiapine fumarate. Patients were discharged on the morning of Day 18 after all clinical assessments had been completed. For Cohort B patients, divalproex sodium was titrated to a target dose of 500 mg bid over a 3-day period and remained at this dose through Day 8. From Day 9 through Day 11, the dose of quetiapine fumarate was initiated and titrated to a daily dose of 150 mg bid. The patients remained on these doses of divalproex sodium (500 mg bid) and quetiapine fumarate (150 mg bid) from Day 11 through Day 16. From Day 17 through Day 19, the doses of divalproex and quetiapine were titrated to no quetiapine and to the patients' pre-study dosing regimens of divalproex sodium. Patients were discharged on the morning of Day 20 after all clinical assessments had been completed. Blood samples for the determination of plasma concentrations of quetiapine and divalproex sodium were collected at specified time periods. For Cohort A, with the administration of quetiapine fumarate on the morning of Day 5 and co-administration of quetiapine fumarate and divalproex sodium on Day 13. For Cohort B, with the administration of divalproex sodium on the morning of Day 8 and co-administration of quetiapine fumarate and divalproex sodium on Day 16.

Mean plasma concentrations of quetiapine measured over the 12-hour periods after administration of the morning doses of trial treatment on Day 5 (quetiapine 150 mg) and Day 13 (quetiapine 150 mg and divalproex 500 mg) is provided in the following figure. The plots of averaged plasma concentrations indicated a trend toward a slightly increased AUCss for quetiapine during co-administration of divalproex.

Fig 1: Mean plasma concentrations of quetiapine



The following table summarizes the statistical evaluation of the pharmacokinetic parameters of quetiapine measured on Day 5 (quetiapine fumarate 150 mg) and Day 13 (quetiapine fumarate 150 mg and divalproex sodium 500mg).

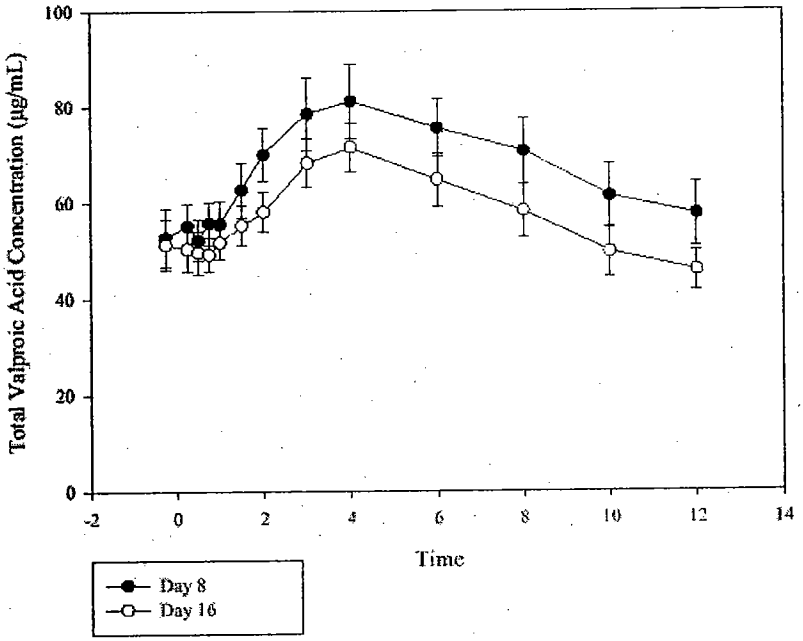
Table 1: Summary of Statistical Analysis for Quetiapine (Quetiapine + Divalproex sodium/Quetiapine)

Parameter	Ratio	90% Confidence Interval (CI)		
		Lower	Upper	
AUC	1.03	0.95	1.12	
Cmax	1.17	0.95	1.43	

Cmax increased by 17% and the 90% CI fell outside the OCPB recommended 80 to 125% confidence limits. The increase in Cmax may not be clinically relevant. Pharmacokinetic parameters for quetiapine in the presence and absence of divalproex sodium indicated that there was no significant change in the extent of exposure (AUCss) of quetiapine when co-administered with divalproex

The mean plasma concentrations of total valproic acid measured over the 12-hour period after administration of the morning doses of trial treatment on day 8 (divalproex 500 mg) and day 16 (divalproex 500 mg and quetiapine 150 mg) are presented in the following figure
The plots of averaged plasma concentrations of valproic acid indicated a trend toward a decreased AUCss and Cmax (ss) for total valproic acid during co-administration of quetiapine fumarate.

Fig. 2: Mean plasma concentrations of total valproic acid



Statistical comparison of the pharmacokinetic parameters of total valproic acid and free valproic acid after morning administration of divalproex sodium 500 mg (Day 8) and after administration of divalproex sodium 500 mg with quetiapine 150 mg (Day 16) are provided in the following tables

Table 2: Summary of Statistical Analysis for Total Valproic Acid (Divalproex + Quetiapine/Divalproex)

Parameter	Ratio	90% Confidence Interval (CI)		
		Lower Limit	Upper Limit	
AUC	0.89	0.84	0.95	
Cmax	0.89	0.84	0.94	

Table 3: Summary of Statistical Analysis for Free Valproic Acid (Divalproex + Quetiapine/Divalproex)

Parameter	Ratio	90% Confidence Interval (CI)		
		Lower Limit	Upper Limit	
AUC	0.90	0.82	0.99	
Cmax	0.88	0.81	0.95	

The concentration of total and free valproic acid decreased by about 11% and 12%, respectively when divalproex was administered with quetiapine compared to when divalproex was administered alone. The 90% CI around the mean ratio for AUC and Cmax were contained within the recommended 80 to 125%. The decrease is not expected to be clinically significant.

Is there a dose/concentration response established for patients with acute mania associated with bipolar disorder?

Concentration/dose response relationship was not established in this efficacy supplement. The maximum dose recommended is similar to that for patients with schizophrenia. However, the dosing regimen is different.

What analytical methods were used to determine the concentration of quetiapine, valproic acid and their metabolites?

Concentrations of quetiapine and its metabolites in plasma were assayed by means of LC MS/MS with liquid-liquid extraction. Concentrations of valproic acid were assayed by mean gas chromatography using flame ionization detection with liquid-liquid extraction. Overall precision for quetiapine QCs was less than or equal to 13.1% and the overall accuracy ranged from 98.5% to 105%. For total valproic acid, overall precision for QCs was less than or equal to 7.41% and the overall accuracy for these QCs, ranged from 102% to 110%. For free valproic acid, overall precision for QCs was less than or equal to 8.71% and the overall accuracy, ranged from 97.5% to 106%. The analytical methods are adequate and acceptable.

General Comments: Co-administration of quetiapine with valproic acid is not expected to cause clinically relevant changes in the pharmacokinetics of either quetiapine or valproic acid. Therefore, dosage adjustments is not recommended when seroquel and divalproex are co-administered. The pharmacokinetics of lithium has been reported in the original NDA not to be affected by co-administration with seroquel. The effect of lithium on quetiapine pharmacokinetics is not known but it is predicted not to be clinically relevant. However, it is suggested that information to validate the lack of an effect of lithium on seroquel pharmacokinetics be provided in the future.

Appendix

Individual Study Report

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Study Title (Study No. 5077IL/0120): An Open Label, Safety, Tolerability and Steady State Pharmacokinetic Drug Interaction Study of the Effect of Co-administered Quetiapine Fumarate (Seroquel™) and Divalproex Sodium (Depakote® Sprinkle) in Patients with Schizophrenic/Schizoaffective Disorders or in Patients with Bipolar Disorder.

Introduction: Quetiapine is an antipsychotic drug belonging to the dibenzothiazepine derivative class. It has been evaluated in the clinic for both adjunct therapy and monotherapy in acute mania associated with bipolar disorder. Divalproex is a delayed-release, enteric-coated formulation of the sodium salt of the branched chain monocarboxylic fatty acid valproic acid (2-propylpentanoic acid). Possible pharmacokinetic interactions between quetiapine and valproic acid have not been explored in humans. It is quite likely that both drugs will be co-administered in manic patients with bipolar disorder, therefore, it is of interest to examine the effect of the combined dosing of divalproex and quetiapine on the pharmacokinetic profiles of both drugs.

Study Objective: The primary objective of this study is to determine that selected pharmacokinetic parameters of quetiapine fumarate (Seroquel™) and divalproex sodium (Depakote ® Sprinkle) measured at baseline do not change during the co-administration of Seroquel and Depakote.

Study Design: This was a multi-center, open label, parallel, two-cohort, drug interaction trial in patients 18 – 60 years old. Nineteen patients with schizophrenic/schizoaffective disorders (Cohort A) and 15 patients (Cohort B) with bipolar disorder and schizoaffective disorder were exposed to study drug to attain 18 evaluable patients from Cohort A and 15 evaluable patients from Cohort B for a total of 33 evaluable patients. The mean age and weight of patients in Cohort A were 40.8 ± 8.92 years and 101.03 ± 18.85 kg, respectively. For Cohort B, the mean age and weight were 41.1 ± 7.83 years and 93.52 ± 32.6 kg, respectively. For Cohort A patients, quetiapine fumarate was titrated to a target dose 150 mg bid over a 5- day period. From Day 6 through Day 8, the dose of divalproex sodium was initiated and titrated to a daily dose of 500 mg bid. The patients remained at these doses of quetiapine fumarate (150 mg bid) and divalproex sodium (500 mg bid) from Day 8 through Day 13. From Day 14 to Day 17, the doses of quetiapine and of divalproex were titrated to no divalproex and to the patients' pre-study dosing regimens of quetiapine fumarate. Patients were discharged on the morning of Day 18 after all clinical assessments had been completed. For Cohort B patients, divalproex sodium was titrated to a target dose of 500 mg bid over a 3-day period and remained at this dose through Day 8. From Day 9 through Day 11, the dose of quetiapine fumarate was initiated and titrated to a daily dose of 150 mg bid. The patients remained on these doses of divalproex sodium (500 mg bid) and quetiapine fumarate (150 mg bid) from Day 11, through Day 16. From Day 17 through Day 19, the doses of divalproex and quetiapine were titrated to no quetiapine and to the patients' pre-study dosing regimens of divalproex sodium. Patients were discharged on the morning of Day 20 after all clinical assessments had been completed. Quetiapine fumarate was administered as oral doses of 25 mg (Batch 7501B) and 100 mg (Batches 7500B and 7536F) tablets. Divalproex sodium was administered orally in 125 mg capsules and was acquired by the individual investigators as commercially-available Depakote Sprinkle.

Blood samples for the determination of plasma concentrations of quetiapine and divalproex sodium were collected. For Cohort A, with the administration of quetiapine fumarate on the morning of Day 5 and co-administration of quetiapine fumarate and divalproex sodium on Day 13, blood samples to determine quetiapine and metabolite (ICI 213,841 and ICI 214,227) plasma concentrations were obtained at 0 (pre-dose, within 15 minutes before dose) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12, hours after dose. Additional samples to assess steady state

pre-dose plasma concentrations of the agents under study were obtained within 15 minutes before dose on Days 3 and 4 (quetiapine only). On Days 11, 12, and 13, two pre-dose samples were collected, one each for quetiapine and valproic acid. For Cohort B, with the administration of divalproex sodium on the morning of Day 8 and co-administration of quetiapine fumarate and divalproex sodium on Day 16, blood samples to determine total and free valproic acid plasma concentrations were obtained at 0 (pre-dose, within 15 minutes before dose) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12, hours after dose. Additional samples to assess steady state pre-dose plasma concentrations of quetiapine and valproic acid were obtained within 15 minutes before dose on Days 6 and 7 (valproic acid only). On Days 14, 15, and 16, two pre-dose samples were collected, one each for valproic acid and quetiapine.

Analytical Methods: Concentrations of quetiapine and its metabolites in plasma were assayed by means of LC MS/MS with liquid-liquid extraction. Concentrations of valproic acid were assayed by mean gas chromatography using flame ionization detection with liquid-liquid extraction. Plasma samples were analyzed for concentrations of quetiapine. The method is a validated procedure with liquid-liquid extraction of quetiapine, ICI 213,841 and ICI 214,227 and their respective internal standards (13 C6-quetiapine, d8-ICI 213,841, and d8-ICI 214,227) from alkalinized human plasma (containing EDTA anticoagulant) using ethyl acetate, followed by reverse-phase liquid chromatography and turbo ionspray ionization tandem mass spectrometry. The method has a calibration range of 0.500 ng/mL to 500 ng/mL, with an applicable quantitation range to 2000 ng/mL by appropriate dilution with plasma. Overall precision for quetiapine QCs, as measured by %RSD, was less than or equal to 13.1% and the overall accuracy ranged from –1.50% to 5.00%. The precision for the dilution integrity QCs was less than or equal to 2.48%, and the overall accuracy ranged from –3.00% to –1.40%. Overall precision for ICI 213,841 QCs, as measured by %RSD, was less than or equal to 12.4% and the overall accuracy, as measured by %RE for these QCs, ranged from –3.50% to 4.00%. The precision for the dilution integrity QCs was less than or equal to 5.60%, and the overall accuracy ranged from –10.3% to 1.10%. Overall precision for ICI 214,227 QCs, as measured by %RSD, was less than or equal to 9.89% and the overall accuracy, as measured by %RE for these QCs, ranged from –5.75% to 7.00%.

Plasma samples were analyzed for concentrations of total valproic acid (VPA). The method is validated with liquid-liquid extraction of VPA and internal standard (cyclohexanecarboxylic acid) from acidified human plasma (containing EDTA anticoagulant) using methylene chloride, followed by gas chromatography with flame ionization detection. The method has a calibration range of 0.500 µg/mL to 140 µg/mL, with an applicable quantitation range to 250 µg/mL by 5-fold dilution with plasma. Accuracy of total VPA from QCs spiked at 1.50, 60.0 and 110 µg/mL ranged from 99.1% to 109%, while precision ranged from 5.42% and 9.27% across 5 days of validation. Accuracy of 102% and precision of 6.24% were obtained at the lower limit of quantitation (0.500 µg/mL). Recovery of total VPA from spiked plasma during method validation averaged 92.0%. Overall precision for QCs, as measured by %RSD, was less than or equal to 7.41% and the overall accuracy, as measured by %Recovery for these QCs, ranged from 102% to 110%.

Plasma samples were analyzed for concentrations of free VPA. The method is a validated procedure with liquid-liquid extraction of free VPA (following ultracentrifugation using Centrifree filters) and internal standard (cyclohexanecarboxylic acid) from acidified human plasma ultrafiltrate (containing EDTA anticoagulant) using methylene chloride, followed by gas chromatography with flame ionization detection. The method has a calibration range of 0.100 to 35.0 µg/mL. Accuracy of free VPA from ultrafiltrate QCs spiked at 0.300, 15.0 and 27.5 µg/mL ranged from 90.9% to 101%, while precision ranged from 3.27% and 7.04%, respectively, across

4 days of validation. Accuracy of 105% and precision of 9.10% were obtained at the lower limit of quantitation (LLOQ, 0.500 µg/mL). Precision of free VPA from plasma QCs spiked at 10.0, 80.0 and 120 µg/mL ranged from 3.49% to 13.8% across 4 days of validation. Overall precision for QCs, as measured by %RSD, was less than or equal to 8.71% and the overall accuracy, as measured by %Recovery for these QCs, ranged from 97.5% to 106%. The analytical methods are adequate and acceptable.

Data analysis: Primary variable for Cohort A: The ratio of AUCss of quetiapine following co-administration of quetiapine fumarate and divalproex sodium on Day 13 to AUCss of quetiapine following administration of quetiapine fumarate alone on Day 5. The ratio of Cmax(ss) of quetiapine following co-administration of quetiapine fumarate and divalproex sodium on Day 13 to Cmax(ss) of quetiapine following administration of quetiapine fumarate alone on Day 5.

The primary variables for Cohort B: The ratio of AUCss of total valproic acid following administration of divalproex sodium and quetiapine fumarate on Day 16 to AUCss of total valproic acid following administration of divalproex sodium alone on Day 8. The ratio of Cmax(ss) of total valproic acid following co-administration of divalproex sodium and quetiapine fumarate on Day 16 to Cmax(ss) of total valproic acid following administration of divalproex sodium alone on Day 8.

Secondary variable for Cohort A: Cmin(ss), tmax, t ½ and CL/F for quetiapine following administration of quetiapine fumarate plus divalproex sodium on Day 13 and that following administration of quetiapine fumarate alone on Day 5. The ratio of AUCss of ICI 213,841 (sulfoxide metabolite of quetiapine) and ICI 214,227 (7-hydroxylated metabolite of quetiapine) following co-administration of quetiapine fumarate and divalproex sodium on Day 13 to AUCss of ICI 213,841 and ICI 214,227 following administration of quetiapine fumarate alone on Day 5. The ratio of Cmax (ss) of ICI 213,841 and ICI 214,227 following co-administration of quetiapine fumarate and divalproex sodium on Day 13 to Cmax (ss) of ICI 213,841 and ICI 214,227 following administration of quetiapine fumarate alone on Day 5. Cmin(ss), tmax, and t ½ for ICI 213,841 and ICI 214,227 following administration of quetiapine fumarate plus divalproex sodium on Day 13 and that following administration of quetiapine fumarate alone on Day 5.

Secondary variables for Cohort B: Cmin(ss), tmax, CL/F and CLr for total valproic acid following administration of divalproex sodium plus quetiapine fumarate on Day 16 and that following administration of divalproex sodium alone on Day 8. The ratio of AUC(ss) of free valproic acid following administration of divalproex sodium and quetiapine fumarate on Day 16 to AUC(ss) of free valproic acid following administration of divalproex sodium alone on Day 8. The ratio of Cmax(ss) of free valproic acid following co-administration of divalproex sodium and quetiapine fumarate on Day 16 to Cmax(ss) of free valproic acid following administration of divalproex sodium alone on Day 8. AUCss , Cmax(ss), Cmin(ss), tmax and CL/F for free valproic acid following administration of divalproex sodium plus quetiapine fumarate on Day 16 and that following administration of divalproex sodium alone on Day 8.

Statistical Analysis: Due to the relatively wide therapeutic windows of quetiapine and valproic acid, the equivalence range for the mean ratios was chosen to be ±30%. AUCss and Cmax (ss) ratios were computed from the respective monotherapy and co-administration log-transformed AUCss or Cmax(ss) parameters. Construction of 90% confidence intervals based upon least-square means from ANOVA model for ratios provided test statistics for equivalence determination. The sponsor indicated that no drug interaction was to be concluded if the 90% confidence intervals of the geometric mean ratios of AUCss and Cmax(ss) were within the

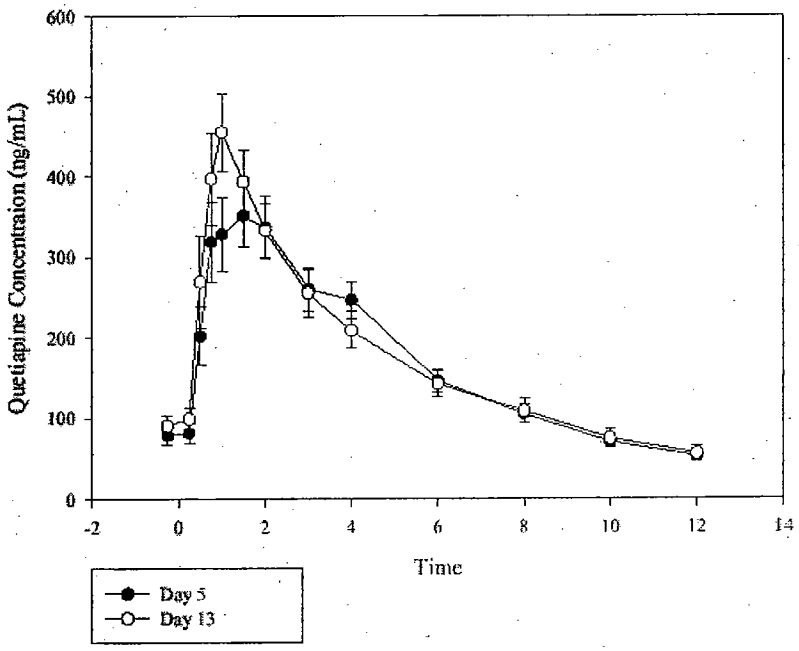
equivalence interval of 0.70 to 1.43. However, the agency recommends that no interaction be concluded if the 90% confidence interval for the mean ratio falls within 0.80 to 1.25.

Pharmacokinetic Results:

Individual and median predose plasma concentrations of each drug showed a trend indicating that steady-state had been achieved by the pharmacokinetic study day.

Mean plasma concentrations of quetiapine measured over the 12-hour periods after administration of the morning doses of trial treatment on Day 5 (quetiapine 150 mg) and Day 13 (quetiapine 150 mg and divalproex 500 mg) is provided in the following figure. The plots of averaged plasma concentrations indicated a trend toward a slightly increased AUCss for quetiapine during co-administration of divalproex.

Fig. 1



Individual values of AUCss and C max(ss) or quetiapine measured on Days 5 and 13 are shown in Figure 2 and Figure 3 respectively.

Fig. 2

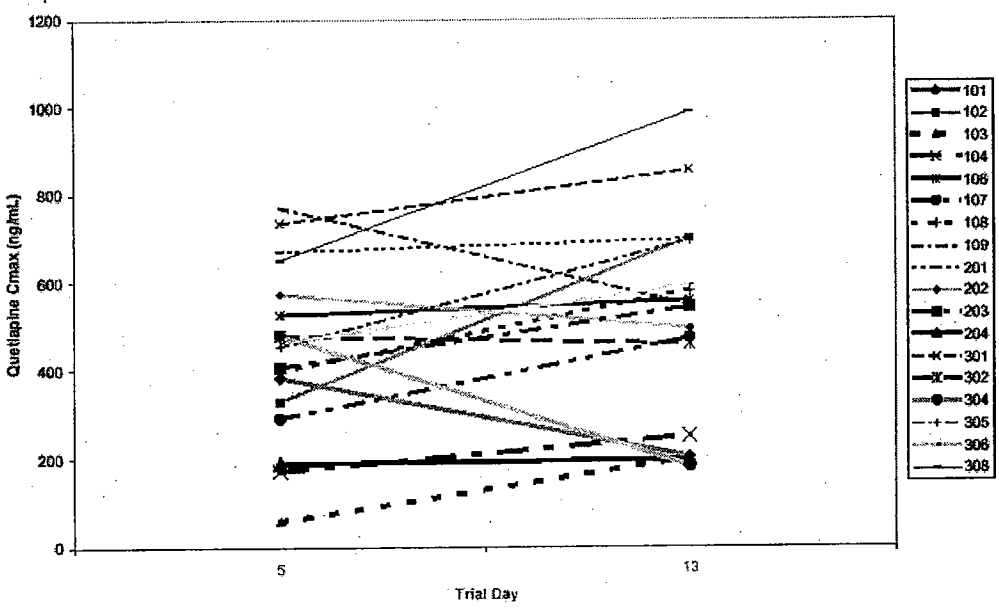


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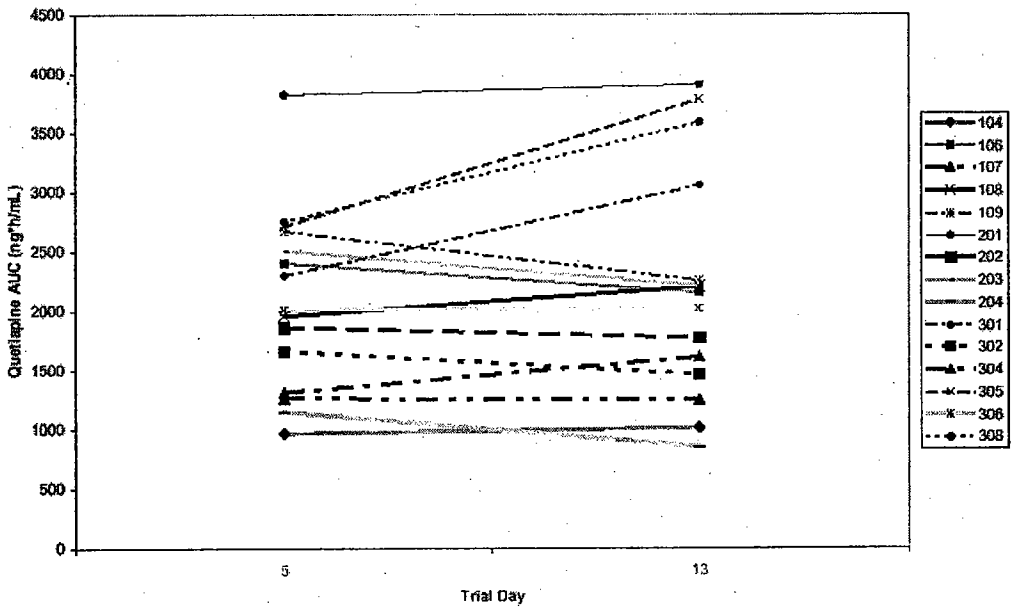
Fig. 3



The following table summarizes the pharmacokinetic parameters of quetiapine measured on Day 5 (quetiapine fumarate 150 mg) and day 13 (quetiapine fumarate 150 mg and divalproex sodium 500mg).

Table 1

Pharmacokinetic Parameter		Quetiapine fumarate	Quetiapine fumarate + Divalproex sodium
AUC(0-12)(ng*h/mL)	Mean	2087.58	2211.12
	SD	764.094	976.12
	CV(%)	36.60	44.12
	Geometric Mean	1954.41	2010.06
	95% CI	1580 – 2418	1556 – 2596
	N	15	15
Cmax (ng/mL)	Mean	445.72	511.50
	SD	194.52	235.07
	CV(%)	43.64	45.96
	Geometric Mean	387.66	45.90
	95% CI	282.94 – 531.14	344.45 – 592.85
	N	18	18
Cmin (ng/mL)	Mean	52.53	60.74
	SD	26.81	38.89
	CV(%)	51.04	64.02
	N	15	15
CL/F (L/h)	Mean	82.39	82.59
	SD	33.30	40.06
	CV(%)	40.4	48.51
	N	15	15

Table 2: Comparison (Quetiapine + Divalproex sodium/Quetiapine)

Parameter	Ratio	90% Confidence Interval (CI)		
		Lower	Upper	
AUC	1.03	0.95	1.12	
Cmax	1.17	0.95	1.43	

A comparison of pharmacokinetic parameters for quetiapine in the presence and absence of divalproex sodium indicated that there was no significant change in the extent of exposure (AUCss) of quetiapine when coadministered with Divalproex. However, Cmax increased by 17% and the 90% CI fell outside the OCPB recommended 80 to 125% confidence limits. The increase in Cmax may not be clinically significant because quetiapine is reported to have a wide therapeutic window.

The following tables provide the statistical comparison of the pharmacokinetic parameters for ICI 213,841 and ICI 214227, the metabolites of quetiapine

Table 3: Statistical comparison of the Pharmacokinetic Parameters of ICI 213,841 after morning administration of quetiapine 150 mg (Day 5) and after administration of quetiapine 150 mg with divalproex 500 mg (Day 13)

Parameter	Ratio	90% Confidence Interval (CI)		
		Lower Limit	Upper Limit	
AUC	1.01	0.96	1.07	
Cmax	1.09	0.90	1.32	

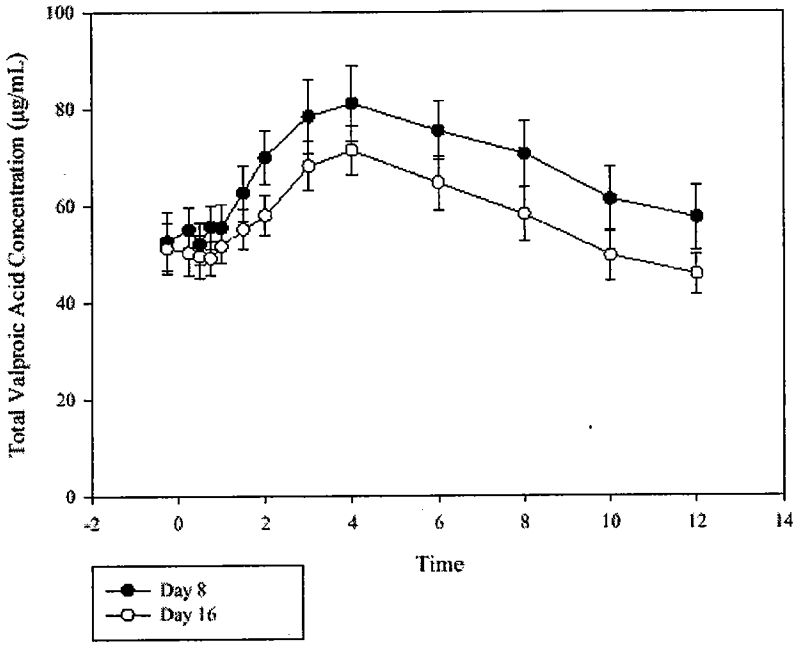
Table 4: Statistical comparison of the Pharmacokinetic Parameters of ICI 214227 after morning administration of quetiapine 150 mg (Day 5) and after administration of quetiapine 150 mg with divalproex 500 mg (Day 13)

Parameter	Ratio	90% Confidence Interval (CI)		
		Lower Limit	Upper Limit	
AUC	1.10	1.03	1.18	
Cmax	1.20	1.02	1.41	

The ICI 213,841 AUCss increased 1% and the Cmax(ss) increased 9% during co-administration of divalproex sodium. The ICI 214,227 AUCss increased 10% and the Cmax(ss) increased by 20% during co-administration with divalproex sodium. The AUCss 90% CI was contained within the recommended 80 to 125% confidence limits. However, Cmax(ss) was outside the recommended limits. It is not expected that the increase in Cmax of ICI 213, 841 or ICI 214,227 will be clinically significant.

The mean plasma concentrations of total valproic acid measured over the 12-hour periods after administration of the morning doses of trial treatment on day 8 (divalproex 500 mg) and day 16 (divalproex 500 mg and quetiapine 150 mg) are presented in the following figure

Figure 4: Mean (SEM) total valproic acid concentrations in Cohort B: Day 8 (divalproex sodium alone) vs day 16 (divalproex sodium and quetiapine)



The plots of averaged plasma concentrations of valproic acid indicated a trend toward a decreased AUCss and Cmax (ss) for total valproic acid during co-administration of quetiapine fumarate.

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Figure 5: Individual AUCss values for total valproic acid: Day 8 (divalproex sodium alone) vs day 16 (quetiapine fumarate and divalproex)

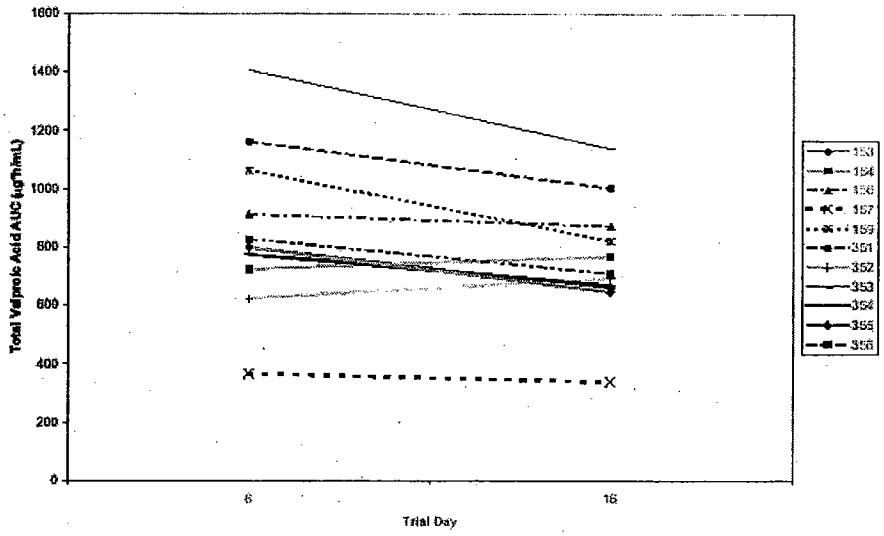

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Figure 6: Individual Cmax(ss) values for total valproic acid: Day 8 (divalproex sodium alone) vs Day 16 (quetiapine fumarate and divalproex sodium)

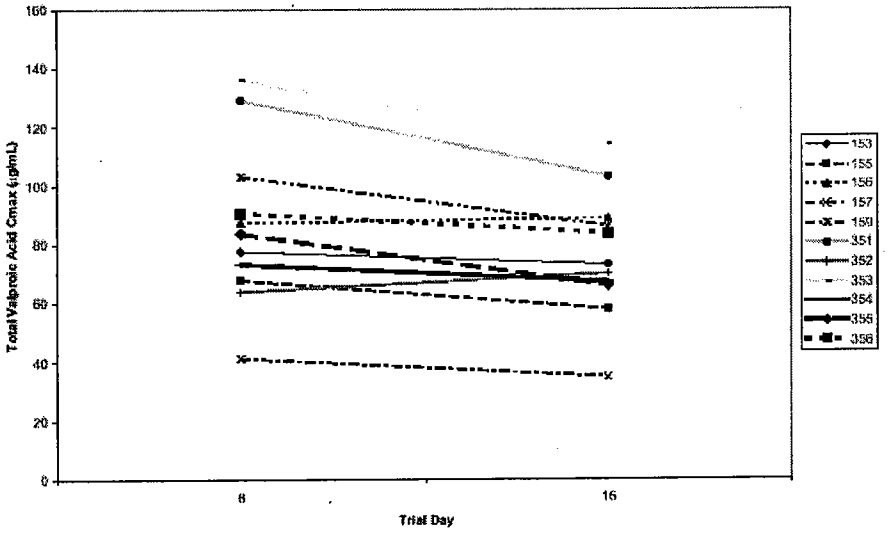

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Table 5: Summary Statistics for Total Valproic Acid Pharmacokinetic Parameter Estimates

Pharmacokinetic Parameter		Divalproex sodium 500mg (Day 8)	Divalproex sodium + Quetiapine fumarate (Day 16)
AUC(0-12)(ng*h/mL)	Mean	859.14	755.81
	SD	276.89	208.65
	CV(%)	32.23	27.61
	Geometric Mean	815.71	726.14
	95% CI	644 – 1033	588.76 – 895.59
	N	11	11
Cmax (ng/mL)	Mean	86.6	76.81
	SD	27.8	21.75
	CV(%)	32.12	28.32
	Geometric Mean	82.48	73.64
	95% CI	66 - 103	59.43 – 91.25
	N	11	11
Cmin (ng/mL)	Mean	57.32	49.21
	SD	23.33	15.69
	CV(%)	40.71	31.88
	N	12	12
CL/F (L/h)	Mean	0.65	0.72
	SD	0.27	0.27
	CV(%)	41.5	37.5
	N	11	11

Table 6: Statistical comparison of the Pharmacokinetic Parameters of total valproic acid after morning administration of divalproex sodium 500 mg (Day 8) and after administration of divalproex sodium 500 mg with quetiapine 150 mg (Day 16)

Parameter	Ratio	90% Confidence Interval (CI)		
		Lower Limit	Upper Limit	
AUC	0.89	0.84	0.95	
Cmax	0.89	0.84	0.94	

Table 7: Statistical comparison of the Pharmacokinetic Parameters of free valproic acid after morning administration of divalproex sodium 500 mg (Day 8) and after administration of divalproex sodium 500 mg with quetiapine 150 mg (Day 16)

Parameter	Ratio	90% Confidence Interval (CI)		
		Lower Limit	Upper Limit	
AUC	0.90	0.82	0.99	
Cmax	0.88	0.81	0.95	

The concentration of total and free valproic acid decreased by about 11% and 12%, respectively when divalproex was administered with quetiapine compared to when divalproex was administered alone. However, the 90% CI were contained within the 80 to 125% recommended

confidence limits for log transformed AUC and Cmax. The decrease is not expected to be clinically significant. The mean percent of dose in urine and the mean renal clearance of valproic acid appeared to increase after co-administration of divalproex sodium and quetiapine fumarate compared to after divalproex sodium monotherapy, the increases were statistically not significant. However, data were available for only 7 patients, inferences regarding the clinical relevance of these findings cannot be made with confidence.

Safety Results: The sponsor reported that the incidences and types of all adverse events and treatment-related adverse events were similar during periods when quetiapine or divalproex were given alone and for when they were co-administered. The incidence of the majority of adverse events was similar, although minor differences were seen with monotherapy with either quetiapine or divalproex compared to co-administration of both agents. Seventeen adverse events were rated as causally related to monotherapy –twenty-two were rated as causally related to combination treatment. All but three adverse events were mild -- events of hypertension, psychosis and vomiting were rated as moderate. Mild decreases in mean platelet concentration was noted, especially in Cohort A which included valproate-naïve patients, but was not accompanied by other clinical signs or symptoms. There were small decreases in the mean diastolic blood pressure and small increases in pulse rate in response to the combination of quetiapine and divalproex compared to monotherapy. These changes were small and were not considered to be clinically significant.

Conclusions: Divalproex sodium does not appear to produce a clinically relevant effect on quetiapine pharmacokinetics. Quetiapine fumarate did not produce a clinically relevant effect on valproic acid pharmacokinetics. Co-administration of quetiapine fumarate and divalproex sodium was reported generally safe and well-tolerated.

Reviewer comments: *The reviewer generally agrees with the sponsor's conclusions. However, there was an increase in Cmax for quetiapine when co-administered with divalproex sodium. The 90% CI for Cmax was not contained within OCPB recommended confidence limits of 80 to 125%. Seroquel is reported to have a wide therapeutic window therefore the increase is not expected to be clinically relevant as evident in the safety summary reported for this study. Valproic acid AUC and Cmax decreased by 10 -12% but the 90% CI were contained within the 80 to 125% confidence limit. However, the 90% CI was on the lower side of the confidence limits. The doses of quetiapine studied were not the maximum recommended doses; however, were within the dosing regimen. This was a parallel study design, which may have contributed to the large variability observed in the data.*

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/s/

Kofi Kumi
6/6/03 01:48:03 PM
BIOPHARMACEUTICS

Raman Baweja
6/6/03 03:14:18 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20—639 SE1-016/017**	**Brand Name**	**Seroquel**
OCPB Division (I, II, III)	**I**	**Generic Name**	**Quetiapine**
Medical Division	**DNDP (HFD-120)**	**Drug Class**	**Psychotropic agent**
OCPB Reviewer	**Kofi Kumi**	**Indication(s)**	**Mono- and adjunct therapy of acute manic episodes associated with bipolar 1 disorder**
OCPB Team Leader	**Raman Baweja**	**Dosage Form**	**25, 100, 200, 300 mg tablets**
		Dosing Regimen	**100 to 800 mg/day**
Date of Submission	**12/30/02**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**9/30/03**	**Sponsor**	**AstraZeneca**
PDUFA Due Date	**10/30/03**	**Priority Classification**	**Standard**
Division Due Date	**9/30/03**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		One study report. 2nd study is by cross-reference to original application.
In-vivo effects of primary drug:	X	2		
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. Need summary of analytical method, including in process controls, used to determine quetiapine and divalproex concentrations in study IL/0120.
QBR questions (key issues to be considered)		**1. Is there clinically significant interaction observed when Seroquel (quetiapine) is administered with Depakote (Divalproex sodium)?**
Other comments or information not included above		**This efficacy supplement is fully electronic. Information in the original application, NDA 20-639, approved on 9/26/199 7 for schizophrenia is cross referenced in this application. The application is for tablet strengths already approved and available commercially. The dosing regimen for the mania indication is different from that approved for schizophrenia but the maximum recommended dose is the same.**
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 20-639 SE1-016/017, HFD-850 (Electronic Entry or Lee), HFD-120, HFD-860 (Baweja, Sahajwalla, Mehta)), CDR (CDR-Biopharm)

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/s/

Kofi Kumi
2/14/03 02:13:02 PM
BIOPHARMACEUTICS

Raman Baweja
2/14/03 02:55:52 PM
BIOPHARMACEUTICS
Filing Memo

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-639/S-016 & S-017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-639 SUPPL # 016 and 017
Trade Name SEROQUEL Generic Name quetiapine
Applicant Name AstraZeneca HFD-120
Approval Date January 12, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1-016, SE1-017

   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 /_X_/ 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 /_X_/ NO /___/

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

SE1-016: THREE

SE1-017: THREE

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

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /_X__/ NO /___/

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

NDA # 20-639

NDA #

NDA #

2. Combination product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_X_/ 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 9:**

(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 /_x__/ 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 /_X_/

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 /_X_/

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:

SE1-016, Investigation #1, Study # 5077IL/0104

SE1-016, Investigation #2, Study # 5077IL/0105

SE1-017, Investigation #1, Study # 5077IL/0099

SE1-017, Investigation #2, Study # 5077IL/0100

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.")

SE1-016 Investigation #1 YES /___/ NO /_x__/

SE1-016 Investigation #2 YES /___/ NO /_x__/

SE1-017 Investigation #1 YES /___/ NO /_x__/

SE1-017 Investigation #2 YES /___/ NO /_x__/

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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?

(c)

SE1-016 Investigation #1 YES /___/ NO /_x__/

SE1-016 Investigation #2 YES /___/ NO /_x__/

SE1-017 Investigation #1 YES /___/ NO /_x__/

SE1-017 Investigation #2 YES /___/ NO /_x__/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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"):

SE1-016, Investigation #1, Study # 5077IL/0104

SE1-016, Investigation #2, Study # 5077IL/0105

SE1-017, Investigation #1, Study # 5077IL/0099

SE1-017, Investigation #2, Study # 5077IL/0100

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?

S-016 Investigation #1 and #2

IND # 32132 YES /_X_/ NO /___/ Explain:

S-017 Investigation #1 and #2

IND # 32132 YES /_X__/ 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 /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ 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 /_x_/

If yes, explain: _____

_____

_____

NOTE APPLICATIONS WERE APPROVED JANUARY 12, 2004

See electronic signature page
Signature of Preparer Date
Doris J. Bates, Ph.D.
Regulatory Project Manager

See electronic signature page
Signature of Office or Division Director Date
Russell G. Katz, M.D.

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347

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/s/

Doris Bates
1/15/04 01:41:20 PM

Russell Katz
1/26/04 08:21:30 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 20-639 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** S-016 & S-017

Stamp Date: December 30, 2002 **Action Date:** January 12, 2004

HFD- 120 **Trade and generic names/dosage form:** Seroquel® (quetiapine fumarate) Tablets

Applicant: AstraZeneca Pharmaceuticals **Therapeutic Class:** Anti-Psychotic

Indication(s) previously approved: Schizophrenia (Adult)

The Agency issued a Written Request to Astrazeneca for this application on February 11, 2003 in which pediatric studies were discussed for both adolescent schizophrenia and pediatric bipolar disorder.

Number of indications for these applications: 2

Indication #1: S-016 Monotherapy for the short-term treatment of acute manic episodes associated with Bipolar I Disorder

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- X **No: Please check all that apply:** X **Partial Waiver** X **Deferred** ____ **Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg** ____	**mo.** ____	**yr.** 0	**Tanner Stage** ____
Max ____	**kg** ____	**mo.** ____	**yr.** 9	**Tanner Stage** ____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- X **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.** 10 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 17 **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 02/11/2008

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Robbin Nighswander, RPh, MS
Supervisory Regulatory Project Manager

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: S-017 Adjunctive Therapy for the short-term treatment of acute manic episodes associated with Bipolar I Disorder

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- X **No: Please check all that apply: __X__Partial Waiver __X__Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg____**	**mo.____**	**yr.__0__**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.__9__**	**Tanner Stage____**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- X **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.** 10 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 17 **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): 02/11/2008

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

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/s/

Robbin Nighswander
1/12/04 02:19:17 PM

DSI CONSULT: Request for Clinical Inspections

Date: February 14, 2003

To: Ni Aye Khin, GCPB Reviewer/HFD-47

Through: Joanne Rhoads, M.D., Director, DSI, HFD-45
Russell Katz, M.D., Director, HFD-120

From: Doris J. Bates, Ph.D., Regulatory Project Manager, HFD-120

Subject: **Request for Clinical Inspections**
NDA 20-639/S-016
AstraZeneca
Seroquel (quetiapine fumarate) Tablets

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. There are four (4) sites, which are all of equivalent priority. DSI should feel free to work with the clinical reviewer, Dr. Robert Levin, to select two or more of these sites to inspect.

The Supplement provides for the following new indication: use of Seroquel as monotherapy in the treatment of acute manic episodes associated with Bipolar I Disorder.

Indication	Protocol #	Site (Name and Address)	Number of Subjects
monotherapy in the treatment of acute manic episodes associated with Bipolar I Disorder	104	Prof. Regina Satkeviciute ZIEGZDRAI Mental Hospital Kaunas Region LT-4313 Lithuania Phone: +370 37 730 480 FAX: +370 37 430 088	24
see above	104	Prof. R. Andrezina Riga Psihoneiirologiska Slimnica Psihiatrijas Katedra Tavika iela 2 1005 Riga, Latvia Phone: +[redacted] (cell phone, 24-7) Phone: +371 70 80 132 (hospital) FAX: +371 70 80 132	24

see above	105	Dr. Sumant Khanna **Study Site:** Dept. of Biological Psychiatry NIMHANS Institute Bangalore 560029 INDIA Phone: +91 80 699 5306 FAX: +91 80 656 4822 **Current Address for Dr. Khanna:** Psychiatry Clinic 63 Paschim Marg Vasant Vihar New Delhi 110 057 INDIA Phone +[redacted] (cell phone)	35
see above	105	Dr. J.K. Trivedi Prof., Dept. of Psychiatry Chhatrapati Shahuji Maharaj Medical University Upgraded King George's Medical College Lucknow 226003 Uttar Pradesh INDIA Phone: +91 522 226 0173 FAX: +91 522 265 1173	28

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

International Inspections:

We have requested inspections because (please check appropriate statements):

____ There are insufficient domestic data

__X__ Only foreign data are submitted to support this application

____ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

____ Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **July 31, 2003**. We intend to issue an action letter on this application by (action goal date) **October 30, 2003**.

Should you require any additional information, please contact Doris J. Bates, Ph.D.

Concurrence: (if necessary)

Thomas P. Laughren, MD, Medical Team Leader

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/s/

Doris Bates
2/20/03 05:28:01 PM

Thomas Laughren
2/24/03 09:51:22 AM

Russell Katz
2/26/03 10:39:36 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: September 26, 2003

TO: Doris Bates, Ph.D., Regulatory Project Manager
Robert Levin, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA #: 20-639/SE1-016

APPLICANT: AstraZeneca

DRUG: Seroquel (quetiapine fumarate) Tablets

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

PROPOSED INDICATION: Monotherapy in Treatment of Acute Mania in Bipolar I Disorder

CONSULTATION REQUEST DATE: February 11, 2003

ACTION GOAL DATE: October 30, 2003

I. BACKGROUND:

Seroquel (quetiapine fumarate) is an atypical antipsychotic agent and is approved in treatment of schizophrenia. In this supplemental NDA, the sponsor requests for the use of Seroquel™ (quetiapine fumarate) Tablets in the Treatment of Acute Manic Episodes Associated with Bipolar I Disorder. The application included the results of protocol 5077IL/0104 and 5077IL/105 entitled "An International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Seroquel™ (Quetiapine Fumarate) and Haloperidol as Monotherapy in the Treatment of Acute Mania."

The study was a multicenter, double-blind, randomized, parallel-group, placebo-controlled

study to compare the effects of quetiapine, haloperidol, and placebo during an acute treatment period (12 weeks) in hospitalized subjects for treatment of an acute manic episode associated with Bipolar I Disorder according to the DSM-IV criteria. Subjects could be discharged from the hospital after Day 7 (ie, on Day 8) if the investigator believed that it was clinically appropriate to discharge, that the subject was not suicidal or homicidal, and that the subject could reasonably be expected to continue in the study on an outpatient basis. Blinded study medication was administered orally, twice a day, beginning on Day 1. Quetiapine treatment began on Day 1 at a dose of 50 to 100 mg/day, with dose escalation thereafter to reach 400 mg/day on Day 4. Quetiapine dose could be increased to 600 mg/day on Day 5 and then adjusted upward over Days 6 to 84, up to 800 mg/day. Haloperidol doses were escalated from 2 mg/day on Day 1 to 4 mg/day on Day 4, with dose increases thereafter to a maximum of 8 mg/day. Dose adjustments were made at the discretion of the investigator based on efficacy, safety, and tolerability.

The primary endpoint for this study was the change from baseline in the Young Mania Rating Scale (YMRS) at Day 21 or last post-baseline visit before Day 21. Maintenance of effect was assessed at 12 weeks. Y-MRS is an 11-item clinician-rated scale used to assess severity of mania in a total score range from 0 (no manic features) to 60 (maximum score). A severity rating is assigned to each item (0-4), based on subjective report of his/her condition over the previous 48 hrs and the clinician's observation during the interview. Four items (irritability, speech, thought content and disruptive/aggressive behavior) are given twice (0-8) the weight of remaining 7 items in order to compensate for poor corporation of severely ill patients.

The protocol was conducted at all non-US sites. Per the Review Division's request, an inspection assignment was issued in April 2003 to evaluate Drs. Satkeviciute and Andrezina's conduct of the protocol 5077IL/0104. These two investigators enrolled a large number of subjects in the protocol.

II. INSPECTIONAL FINDINGS

The following sites were inspected:

NAME	Location	Protocol	Assignment Date	EIR received Date	Classification
Prof. Satkeviciute (Center 324)	Kaunas, Lithuania	5077IL/0104	4/16/03	9/4/03	NAI
Prof. Andrezina (Center 331)	Riga, Latvia	5077IL/0104	4/16/03	8/7/03	VAI

Prof. Satkeviciute, M.D.

At this site, 27 subjects were screened and 24 subjects were randomized in protocol 5077IL/0104. 14 subjects discontinued from the study. 10 subjects completed the study.

An audit of 11 subjects' records was conducted. All subjects signed the informed consent. No Form FDA-483 was issued. Based on the limited information provided in the EIR, no major

objectionable conditions noted. Overall, data appear acceptable.

Prof. Andrezina, M.D.

At this site, 24 subjects were enrolled in protocol 5077IL/0104. Five subjects discontinued from the study. No SAE reported during the study.

An audit of 6 subjects' records was conducted. Inspectional findings included protocol violations:

1) Subject 545 had a YMRS score of 27 with a score of 4 only in speech at randomization, yet, this subject was enrolled in the study.
2) Subject 550 was given lorazepam 5 mg/day on days 6-10 during the study.

In the EIR, it was stated that these two subjects were already excluded from data analysis according to the sponsor representative. The review division to check this issue in the database. Overall, data appear acceptable .

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As mentioned above, there was protocol violation of 2 subjects at Dr. Andrezina's site. Overall, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol and amendments. The data from for the study sites that were inspected appear acceptable for use in support of this supplemental NDA.

Limitation to the inspections: the source documents were written either in Lithuanian or Latvian.

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection completed but EIR still pending

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Khin Maung U, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

cc:
NDA 20-639/SE1-016
Division File/Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/U
HFD-46/Khin
HFD-46/Friend
HFD-46/George GCPB1 Files

rd: NK:9/26/03

O:\NK\CIS\NDA20639SE1016 Seroquel Mania Mono CIS.doc

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

/s/

Ni Aye Khin
9/29/03 09:05:19 AM
MEDICAL OFFICER

Khin U
9/29/03 09:51:28 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Raisa Andrezina, M.D.
Riga Psihoneiirologiska Slimnica
Psihiatrijas Katedra
Tavika iela 2
1005 Riga, Latvia

AUG 18 2003

Dear Professor Andrezina:

Between July 14 and 16, 2003, Ms. Alicia M. Mozzachio, representing the United States (U.S.) Food and Drug Administration (FDA), conducted an investigation and met with you and your coinvestigators, Drs. [ ], to review your conduct of a clinical investigation (protocol 5077IL/0104 entitled "An International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Seroquel™ (Quetiapine Fumarate) and Haloperidol as Monotherapy in the Treatment of Acute Mania") of the investigational drug Quetiapine Fumarate (Seroquel), performed for AstraZeneca. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

We understand that you did not conduct this study under a U.S. Investigational New Drug Application (IND). For future reference, however, we are providing comments so that you will be aware of FDA's requirements for clinical studies conducted under an IND.

We provide these comments based on our review of the establishment inspection report and the documents submitted with that report. The provision of the U.S. Code of Federal Regulations (CFR) that would have been violated had the study been conducted under an IND is provided for future reference. We are aware that at the conclusion of the inspection, Ms. Mozzachio's discussion with you included the following:

1. You did not adhere to the investigational plan [21 CFR 312.60].

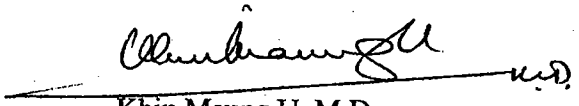
   a. One of the protocol-specified inclusion criteria was a Young Mania Rating Scale (YMRS) score of at least 20 at both screening and randomization, including a score of at least 4 on two of the following YMRS items – irritability, speech, content and disruptive/aggressive behavior. Subject 545 had a YMRS score of 27 with a score of 4 in speech only at randomization; however, this subject was enrolled in the study.

   b. The protocol allowed the administration of lorazepam up to 4mg/day on days 5-7 and up to 2 mg/day on days 8-10. Subject 550 was administered lorazepam 5 mg/day on days 6-10 during the study.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Mozzachio during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,



Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003996189
Field Classification: Refer to Center
Headquarters Classification:
_____1)NAI
__X__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__X__ failure to adhere to protocol (05)

cc:
HFA-224
HFD-120 Doc.Rm. NDA 21-639/SE1-016
HFD-120 Review Div.Dir. Katz
HFD-120 MO Levin
HFD-120 PM Bates
HFD-46 c/r/s GCP File #10965
HFD-46 MO Khin
HFD-46 CSO Friend
HFR-CE650 DIB Baumgarten
HFR-CE6520 BIMO Yuscius
HFR-CE600 Field Investigator Mozzachio
HFC-134 Kadar
GCF-1 Seth Ray

r/d:NK(8/13/03)
reviewed:KMU(8/13/03)
f/t:sg(8/13/03)
O:\NK_Letters\Andrezina.vai.doc

Reviewer Note to Rev. Div. M.O.

- At this site, 24 subjects were enrolled in protocol 5077IL/0104. Five subjects discontinued from the study. No SAE reported during the study.
- An audit of 6 subjects' records was conducted.
- Limitation to this inspection: the source documents were written in Latvian.
- Inspectional findings included:
  Protocol violations
  1) Subject 545 had a YMRS score of 27 with a score of 4 only in speech at randomization, yet, this subject was enrolled in the study.
  2) Subject 550 was given lorazepam 5 mg/day on days 6-10 during the study.
- In the EIR, it was stated that these two subjects were already excluded from data analysis according to the sponsor representative. The review division to check this issue in the database.
- Overall, data appear acceptable.

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

/s/

Khin U
8/28/03 08:26:11 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Regina Satkeviciute, M.D.
Ziegzdriai Mental Hospital
Kaunas Region
LT-4313 Lithuania

OCT - 7 2003

Dear Professor Satkeviciute:

Between July 14 and 16, 2003, Ms. Melissa J. Garcia, representing the United States (U.S.) Food and Drug Administration (FDA), conducted an investigation and met with you and your coinvestigators, Drs. [ ], to review your conduct of a clinical investigation (protocol 5077IL/0104 entitled "An International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Seroquel™ (Quetiapine Fumarate) and Haloperidol as Monotherapy in the Treatment of Acute Mania") of the investigational drug Quetiapine Fumarate (Seroquel), performed for AstraZeneca. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Garcia during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003996185
Field Classification: NAI
Headquarters Classification:
__X _1)NAI
__ __2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-120 Doc.Rm. NDA 20-639/SE1-016
HFD-120 Review Div.Dir. Katz
HFD-120 MO R. Levin
HFD-120 PM D. Bates
HFD-46 c/r/s GCP File #10976
HFD-46 MO Khin
HFD-46 CSO Friend
HFR-CE250 DIB Wagner
HFR-CE250 BIMO Salisbury
HFR-CE250 Field Investigator Garcia
HFC-134 Kadar
GCF-1 Seth Ray

r/d:NK(9/23/03)
reviewed:KMU(9/24/03)
f/t:sg(9/24/03)
O:\NK_Letters\Satkeviciute.nai.doc

Reviewer Note to Rev. Div. M.O.

- At this site, 27 subjects were screened and 24 subjects were randomized in protocol 5077IL/0104. 14 subjects discontinued from the study. 10 subjects completed the study.
- An audit of 11 subjects' records was conducted.
- All subjects signed the informed consent.
- No Form FDA-483 was issued.
- Based on the limited information provided in the EIR, no major objectionable conditions noted.
- Overall, data appear acceptable.

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/s/

Khin U
10/10/03 04:14:29 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: September 26, 2003

TO: Doris Bates, Ph.D., Regulatory Project Manager
Robert Levin, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA #: 20-639/SE1-017

APPLICANT: AstraZeneca

DRUG: Seroquel (quetiapine fumarate) Tablets

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

PROPOSED INDICATION: Add-on therapy in Treatment of Acute Mania in Bipolar I Disorder

CONSULTATION REQUEST DATE: February 11, 2003

ACTION GOAL DATE: October 30, 2003

I. BACKGROUND:

Seroquel (quetiapine fumarate) is an atypical antipsychotic agent and is approved in treatment of schizophrenia. In this supplemental NDA, the sponsor requests for the use of Seroquel™ (quetiapine fumarate) Tablets as add-on therapy in Acute Manic Episodes Associated with Bipolar I Disorder. The application included the results of protocol 5077IL/0099 designed as a randomized, double-blind, placebo-controlled study using quetiapine as add-on therapy with lithium or divalproex. Subjects with a DSM-IV diagnosis of bipolar I disorder and display an acute mania as most recent episode were included in the study. The primary study objective was to compare the efficacy and safety of quetiapine used as add-on therapy with lithium or

divalproex for the treatment of acute mania in subjects with bipolar I disorder.

The primary efficacy endpoint was change from baseline to week 3 in the total Young Mania Rating Scale (Y-MRS) scores. Therapeutic blood level of mood stabilizers on days 4, 7, 10, 14 and 21: target trough lithium concentration of 0.7-1.0 meq/l or valproate of 50-100 ug/ml were measured during the study. The protocol recommends serum concentrations of mood stabilizers reflect trough level, i.e., within 2 hours prior to the next scheduled dose of mood stabilizer.

Per the Review Division's request, an inspection assignment was issued in February 2003 to evaluate Drs. conduct of the protocol 5077IL/0099. These two investigators enrolled a large number of subjects in the protocol.

II. INSPECTIONAL FINDINGS

The following sites were inspected:

NAME	Location	Protocol	Assignment Date	EIR received Date	Classification
Dr. Bari (Center 07)	Chula Vista, CA	5077IL/0099	2/20/03	5/13/03	VAI
Dr. Goenjian (Center 38)	Long Beach, CA	5077IL/0099	2/20/03	4/14/03	VAI

BARI, M.D.

This clincial investigator conducts research and practices Synergy Clinical Research Center, 450 Fourth Avenue Suite 409,Chula Vista, CA 91910. The study took place at Bayview Hospital, 300 Moss Street, Chula Vista, CA.

For the study, 18 subjects were randomized at this site. A total of 7 subjects completed the study and 11 subjects discontinued. Reasons for discontinuation included withdrawal of consent (9 subjects), lack of efficacy (1 subject) and subject 1077 refused visit 7 assessment.

An audit of 10 subjects' records was conducted. Inspectional findings included: 1) blood sample was collected for mood stabilizer (valproic acid level) from subject 1077 two hours post-dose for two occasions during the study, instead of 10-12 hours after administration according to the protocol; 2) the site did not maintain adequate and accurate records in that for subject 1118, there was no documentation in source document that vital signs were done on 2/17/01 while blood pressure and pulse were recorded in the case report form.

All subjects signed the informed consent. Overall, data appear acceptable.

GOENJIAN, M.D.

This clinical investigator conducts research and practices medicine at CNS Network, 12772 Valley View St, Garden Grove, CA and 4510 East Pacific Coast Hwy, Long Beach, CA. The study took place at Pacific Hospital, 2776 Pacific Ave, Long Beach, CA.

For the study, 15 subjects were screened; 3 subjects were screen failures and 12 subjects were

randomized. A total of 5 subjects completed the study and 7 subjects discontinued. Reasons for discontinuation included lack of efficacy or at PI's discretion.

An audit of all 15 subjects' records was conducted. No FDA-483 was issued. However, one subject (1170) did not have the screening laboratory tests prior to randomization.

All subjects signed the informed consent. Overall, data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As mentioned above, there was the issue of collection time of valproic acid level from subject 1077 at Dr. Bari's site and subject 1170 did not have the screening laboratory tests prior to randomization at Dr. Goenjian's site. Overall, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol and amendments. The data from for the study sites that were inspected appear acceptable for use in support of this supplemental NDA.

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection completed but EIR still pending

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Khin Maung U, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

cc:
NDA 20-639/SE1-017
Division File/Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/U
HFD-46/Khin
HFD-46/Friend
HFD-46/George GCPB1 Files

rd: NK:9/26/03

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/s/

Ni Aye Khin
9/29/03 09:10:21 AM
MEDICAL OFFICER

Khin U
9/29/03 10:00:16 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Armen Goenjian, M.D.
12772 Valley View Street
Suite 3
Garden Grove, California 92845

APR 23 2003

Dear Dr. Goenjian:

Between March 13 and 27, 2003, Mr. Ronald L. Koller representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # 5077IL/0099 entitled: "A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of the Safety and Efficacy of Seroquel™ (Quetiapine Fumarate) as Add-on Therapy with Lithium or Divalproex in the Treatment of Acute Mania") of the investigational drug quetiapine (Seroquel), performed for AstraZeneca. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Koller presented and discussed with you the inspectional observations. We wish to emphasize that for subject 1170, you did not obtain screening laboratory tests prior to randomization as required per protocol (21 CFR 312.60).

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Koller during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Antoine El-Hage

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003936441
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__X _2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
_X_failure to adhere to protocol (05)

cc:
HFA-224
HFD-120 Doc.Rm. NDA#20-639/SE1-017
HFD-120 Review Div.Dir. Katz
HFD-120 MO Levin
HFD-120 PM Bates
HFD-47c/r/s/ GCP File #10870
HFD-47 MO Khin
HFD-47 CSO Friend
HFR-PA252 DIB Stokke
HFR-PA2565 Bimo Monitor & Field Investigator Koller
GCF-1 Seth Ray

r/d: (NK): 4/18/03
reviewed:AEH: 4/21/03
f/t:ml: 4/21/03

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Reviewer Note to Rev. Div. M.O.

- PI conducts research and practices medicine at CNS Network, 12772 Valley View St, Garden Grove, CA and 4510 East Pacific Coast Hwy, Long Beach, CA. The study took place at Pacific Hospital, 2776 Pacific Ave, Long Beach, CA.
- For the study (protocol 5077IL/0099), 15 subjects were screened; 3 subjects were screen failures and 12 subjects were randomized. A total of 5 subjects completed the study and 7 subjects discontinued. Reasons for discontinuation included lack of efficacy or at PI's discretion.
- An audit of all 15 subjects' records was conducted.
- No FDA-483 was issued. However, one subject (1170) did not have the screening laboratory tests prior to randomization.
- All subjects signed the informed consent.
- Overall, data appear acceptable.

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/s/

Antoine El-Hage
5/5/03 02:27:43 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Mohammed Bari, M.D.
Synergy Clinical Research Center
450 Fourth Avenue
Suite 409
Chula Vista, California 91910

JUN 12 2003

Dear Dr. Bari:

Between April 7 and 17, 2003, Mr. Thomas R. Beilke, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # 5077IL/0099 entitled: "A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of the Safety and Efficacy of Seroquel™ (Quetiapine Fumarate) as Add-on Therapy with Lithium or Divalproex in the Treatment of Acute Mania") of the investigational drug quetiapine (Seroquel), performed for AstraZeneca. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Beilke presented and discussed with you Form FDA 483, the Inspectional Observations. We wish to emphasize that subject 1077 blood samples for valproic acid were collected at two hours post-dose on two occasions. The protocol states blood samples for mood stabilizer to be drawn approximately 10 to 12 hours after administration if treatment is given twice daily (21 CFR 312.60).

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Beilke during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Antoine El-Hage

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003189819
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__X _2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
_X_ failure to adhere to protocol (05)

cc:
HFA-224
HFD-120 Doc.Rm. NDA#20-639/SE1-017
HFD-120 Review Div.Dir. Katz
HFD-120 MO Levin
HFD-120 PM Bates
HFD-47c/r/s/ GCP File #10270
HFD-47 MO Khin
HFD-47 CSO Friend
HFR-PA252 DIB Stokke
HFR-PA2565 Bimo Monitor Koller
HFR-PA2535 Field Investigator Beilke
GCF-1 Seth Ray

r/d: (NK): 5/28/03
reviewed:AEH: 5/29/03
f/t:ml: 6/3/03

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Reviewer Note to Rev. Div. M.O.

- PI conducts research and practices Synergy Clinical Research Center, 450 Fourth Avenue Suite 409,Chula Vista, CA 91910. The study took place at Bayview Hospital, 300 Moss Street, Chula Vista, CA.
- For the study (protocol 5077IL/0099), 18 subjects were randomized at this site. A total of 7 subjects completed the study and 11 subjects discontinued. Reasons for discontinuation included withdrawal of consent (9 subjects), lack of efficacy (1 subject) and subject 1077 refused visit 7 assessment.
- An audit of 10 subjects' records was conducted.
- Inspectional findings: 1) blood sample was collected for mood stabilizer (valproic acid level) from subject 1077 two hours post-dose for two occasions during the study, instead of 10-12 hours after administration according to the protocol; 2) PI did not maintain adequate and accurate records in that for subject 1118, there was no documentation in source document that vital signs were done on 2/17/01 while blood pressure and pulse were recorded in the case report form.
- All subjects signed the informed consent.
- Overall, data appear acceptable.

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

/s/

Antoine El-Hage
6/20/03 06:12:11 AM

Bates, Doris J

From: Bates, Doris J
Sent: Tuesday, November 25, 2003 3:23 PM
To: 'DeFeo, Pat A'
Cc: Bates, Doris J
Subject: RE: NDA 20-639, S-016 and S-017: Complete Class I Responses Acknowledged.

Good afternoon Pat:

This e-mail confirms that your submissions of November 11, 2003, to NDA 20-639 S-016 and S-017, received November 12, 2003, are complete, class 1 responses to our action letter of October 27, 2003.

We also note with thanks your secure e-mail transmission of November 18, 2003, which corrected a typographical error in the labeling for these submissions.

Because the submissions were received on November 12, 2003, their two month action due date is January 12, 2004. At this time, we have no additional questions related to your resubmissions.

Please feel free to contact me at 301-594-5536 or by return email if you have any questions.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doris Bates
11/25/03 03:24:50 PM
signed into DFS following transmission to firm via secure e-mail.

Minutes of Meeting
NDA 20-639 / SE1-016, -017
Seroquel (quetiapine) Tablets
AstraZeneca: Bipolar Disorder, Monotherapy (S-016) and [ ] Therapy (S-017)
Supplemental NDA Filing Meeting Minutes

DATE: February 11, 2003
INPUT RECEIVED FROM: R. Katz, T. Laughren, R. Levin, T. Podruchny, T. Oliver, D. Klein, K. Jin, K. Mahjoob, R. Baweja, K. Kumi, L. Stockbridge, N. Khin, D. Bates

Background: Quetiapine is currently approved for the short-term treatment of schizophrenia. The current pair of supplements provides for its use in the monotherapy and adjunctive therapy of acute manic episodes associated with bipolar I disorder. (One monotherapy trial included haloperidol as an active comparator, noteworthy because this drug is not presently approved for the treatment of bipolar disorder. The adjunctive therapy trials utilized lithium or valproate as concomitant medication.) The applicant is also developing quetiapine in the maintenance treatment of bipolar disorder but this program is presently in Phase 2.

Summary: The supplemental NDA is an all-electronic submission and was found fileable in all pertinent disciplines. It is classified 6S (approved chemical entity, new indication, standard priority). The receipt date was December 30, 2002; the filing date is February 28, 2003. The action due date is October 30, 2003. This action will require Dr. Katz' signature. All reviews should be completed by early September, 2003.

Discussion: The following minutes summarize information received in person and online.

- *CMC:* Fileable; review is limited to evaluation of an EA (consult sent to N. Sager by D. Klein).
- *Pharm/Tox:* No P/T review is needed; no new pharm/tox data or labeling.
- *Clin Pharm/Biopharmaceutics:* Fileable. The supplements include PK data. Adjunctive therapy trials included lithium or valproate. A divalproex interaction is described in the proposed labeling; the language is new. The OCPB reviewer needs information from the applicant regarding assay methodology for quetiapine and divalproex blood levels in one study (to include in 74-day letter).
- *Clinical:* Fileable, no significant issues identified.
- *DSI:* A DSI audit will be performed for US sites in connection with S-017 and internationally for S-016. A consult will be prepared for the international sites.
- *Statistics:* Fileable.
- *DDMAC:* No filing issues identified.
- *Regulatory / Project Management (with Post Meeting Notes):* All team members have EDR access. The firm paid two User Fees to cover monotherapy and adjunctive therapy separately. The firm requested a deferral of the requirement for pediatric studies, as per prior agreement with the Agency (May 17, 2001 Guidance Meeting). The 74-day acknowledgement/filing letter for the supplement will address these points and include the review question from OCPB.

The supplemental NDAs were officially filed as of this date. The firm's representative was contacted by phone following the meeting and informed of the filing.

Post Meeting Notes: 74-day letter transmitted to the firm on Day 72, March 11, 2003 (e-mail).

Please see electronic signature page

Doris J. Bates, Ph.D.
Regulatory Project Manager
For the attendees

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/s/

Doris Bates

7/30/03 04:49:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

SUPPLEMENTAL NDAs
ACKNOWLEDGED / FILED:
NO FILING ISSUES IDENTIFIED
REVIEW ISSUE (BIOPHARMACEUTCS)

NDA 20-639 / S-016, S-017

AstraZeneca Pharmaceuticals LP
Attention: Mr. Gerald Limp
1800 Concord Pike / PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp:

Please refer to your December 30, 2002 supplemental new drug applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SEROQUEL (quetiapine). These supplements, NDA 20-639 / S-016 and S-017, provide for the use of quetiapine as monotherapy (S-016) and as adjunctive therapy (S-017) in the treatment of acute manic episodes associated with bipolar I disorder.

We also note your amendments of January 16, 2003, to these supplemental NDAs.

User Fee Payment and Filing Date. Your payments of the User Fees were complete as of December 20, 2002 (UFID# 4487 for S-016 and 4488 for S-017). The official date for these applications to be filed under section 505(b) of the Act was February 28, 2003, in accordance with 21 CFR 314.101(a).

Action Date: The action date for both supplemental applications is October 30, 2003.

Review and Filing Issues.
We have completed our filing reviews of your applications, as amended. As you were notified (telephone conversation with Patricia deFeo, February 11, 2003), your submissions were filed, effective on that date.

In our filing review, we have identified the following review issue, and we request that you submit information as described below:

Clinical Pharmacology and Biopharmaceutics: Please provide a summary of the analytical method, including any associated in-process controls, used to determine the quetiapine and divalproex concentrations in study IL/0120.

You should be aware that our filing review is only a preliminary evaluation of the applications. Additional deficiencies may be identified during our substantive review of your applications, and issues may be added, deleted, expanded upon, or otherwise modified as the review progresses.

At this time, we request that you respond to the above request 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 the response is received.

Pediatric Studies: Deferral; Status of Pediatric Rule. Your sNDAs include a request for deferral of pediatric studies, as agreed by the Division in advance of sNDA submission (Guidance Meeting, May 17, 2001). The Division confirms this prior agreement.

As you are aware, FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court during calendar year 2002. On October 17, 2002, the court ruled that FDA did not have authority to issue the Pediatric Rule and barred FDA from enforcing it.

The Division of Health and Human Services (DHHS) has decided not to pursue an appeal of this decision in the courts. However, DHHS intends to work with Congress in an effort to enact legislation that will require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third parties have decided to appeal the court decision striking down the rule. Therefore, although the Pediatric Rule as originally promulgated is no longer in force, the deferral previously granted by the Division remains appropriate pending reinstatement of a regulatory requirement for the conduct of pediatric studies.

You should also note that the pediatric exclusivity provisions of FDAMA, as reauthorized by the Best Pharmaceuticals for Children Act, are distinct from the Pediatric Rule, and thus not affected by the court ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for further details.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 594-2850, or contact her via e-mail at batesd@cder.fda.gov.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
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