Team Leader Review Memo

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

1. Introduction and Background

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

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

2. CMC

There are no unresolved CMC issues.

3. Nonclinical Pharmacology/Toxicology

There are no unresolved Pharmacology/Toxicology issues.

4. Clinical Pharmacology/Biopharmaceutics

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

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

5. Clinical and Statistical

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

5.1 Objective of the Studies

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

5.2 Definition of Relapse

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

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

5.3 Subject Selection

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

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

5.4 Study Design

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

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

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

Randomized Withdrawal Phase:

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

5.5 Efficacy Findings

5.5.1 Baseline Features

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

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

5.5.2 Primary Efficacy Results

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

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

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

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

Table 2 Summary of Subjects with Mood Event and Censored Patients

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

Source: George Kordzakhia, Ph.D.

Statistical Reviewer's Findings

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

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

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

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

6 Safety Findings

6.1 Exposure

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

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

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

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

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

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

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

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

7Labeling

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

8. DSI Audits

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

9. Conclusions and Recommendations

9.1 Recommended Regulatory Action

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

9.2 Postmarketing Studies (under PREA, Subpart H)

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

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

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

cc: NDA 20-639
HFD 130
T Laughren
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