

## Cross-Discipline Team Leader Review Memo

<b>Date</b>	<i>{See Appended Electronic Signature Page}</i>
<b>From</b>	Ni A. Khin, M.D. Lead Medical Officer Division of Psychiatry Products, HFD-130 Office of Drug Evaluation I, Office of New Drugs (OND) Center for Drug Evaluation and Research (CDER)
<b>Subject</b>	Cross-Discipline Team Leader (CDTL) Review
<b>NDA#</b>	NDA 20-639/S-057 (Seroquel) NDA 22-047/S-029 (Seroquel XR)
<b>Applicant Name</b>	AstraZeneca
<b>Date of Submission/Received Date</b>	October 31, 2012
<b>PDUFA Goal Date</b>	April 30, 2013
<b>Proprietary Name / Established Name</b>	Quetiapine (Seroquel) Quetiapine extended-release (Seroquel XR)
<b>Dosage Forms / Strength</b>	25, 50, 100, 200, 300 and 400 mg immediate release oral tablets 50, 150, 200, 300 and 400 mg extended release oral tablets
<b>Proposed Indication(s)</b>	Bipolar Depression: Study Results to be included in Pediatric Use Section of the Labeling
<b>Recommended Action:</b>	Approval

### 1. INTRODUCTION

Quetiapine is an atypical antipsychotic agent initially approved for treatment of schizophrenia in 1997. Based on results from short-term placebo controlled studies in adults, seroquel is also approved for the treatment of bipolar depression in October 2006, and Seroquel XR for the same indication in October 2008. At the time of these approvals, pediatric studies under PREA for Seroquel/Seroquel XR were deferred. For Seroquel XR, the approval letter indicated that the final clinical study report for a pediatric study for the use of Seroquel XR monotherapy in the treatment of bipolar depression be submitted by 6/1/2015.

In this set of NDA supplement submission, the sponsor has included results from a pediatric clinical study (D144AC00001) entitled “An 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study of the efficacy and safety of quetiapine fumarate extended-release (Seroquel XR) in children and adolescent subjects with bipolar depression”.

The team who conducted review of this set of supplement in the first review cycle consisted of:

<b>Material Reviewed/Consulted</b>	<b>Name of discipline reviewers</b>
Clinical Review	Cara Alfaro, Pharm.D.
Statistical Review	George Kordzakhia, Ph.D.
Office of Scientific Investigations	John Lee, M.D.
Others: OPDP SEALD/OND PMHS/OND	Jessica Cleck Derenick, Ph.D. Debra Beitzell Elizabeth Durmowicz, M.D.

A complete response (CR) action letter was sent to the Sponsor on August 6, 2012, indicating the sponsor’s effort to revise the clinical study report (CSR) to ensure the quality of final study report.

On October 29, 2012, the sponsor submitted the corrected CSR in response to our CR letter. Dr. Alfaro reviewed this submission (review dated 3/22/13).

## **2. BACKGROUND**

The IND program of quetiapine extended-release in bipolar depression was developed under IND#76,146 by AstraZeneca.

### **3.0 CHEMISTRY, MANUFACTURING AND CONTROL (CMC)**

There is no new CMC information.

### **4.0 NON-CLINICAL PHARMACOLOGY/TOXICOLOGY**

There is no new pharmacology or toxicology information.

### **5.0 CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS**

No new clinical pharmacology study data in this submission. However, the OCP asked the sponsor to revise the PK section of the label using forest plots. Additionally, Islam Younis, Ph.D., conducted a review of sponsor's pharmacometric PK-PD modeling data using pooled efficacy data from short-term studies in pediatric and adults with seroquel IR and seroquel XR.

### **6.0 CLINICAL MICROBIOLOGY**

Not applicable.

### **7.0 CLINICAL/STATISTICAL - EFFICACY**

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

In this set of NDA supplement, the sponsor proposes to include the results from a failed 8-week, placebo-controlled clinical study of quetiapine extended release (150-300 mg/day) in children and adolescents aged 10-17 with bipolar depression (Study # D144AC00001) in the pediatric use section.

I have already described this study in my prior CDTL memo dated 7/16/12. I would briefly summarize the results again in the subsections below.

#### **7.2 Summary of Studies Pertinent to Efficacy (b) (4) in Treatment of Schizophrenia**

##### **7.2.1 Study D144AC00001**

This study was a 8 week, multicenter, randomized, double-blind, placebo controlled, parallel-group, safety and efficacy study of quetiapine extended release (150-300 mg/day) in children and adolescent patients (aged 10-17 yrs) who met the diagnosis of bipolar I or II according to the DSM-IV-TR criteria, with current episode depressed confirmed by K-SADS-PL. Following a 7 to 28 day

wash out period, eligible patients were randomized (1:1) to quetiapine XR or placebo within age strata (10 to 12 years, 13 to 17 years). Study medication was administered orally, once daily in the evening. Quetiapine XR was administered as follows: 50 mg on day 1, 100 mg on day 2, 150 mg on day 3 and continued until week 2 or 3. If at 2 or 3 weeks, there was a deterioration defined as Clinical Global Impressions for Bipolar Disorder – Change from Preceding Phase (CGI-BP-C)  $\geq 5$ , then the dose of quetiapine XR or placebo was increased to 300 mg/day: increase to 200 mg, then increase to 250 mg one day later, then increase to 300 mg one day later and maintain if subject's symptoms had stabilized. If the dose had not been increased from 150 to 300 at weeks 2 or 3, it was to be increased to 300 mg (following the same titration) at week 4 or later if the patient had a clinical deterioration or no improvement defined as Clinical Global Impressions for Bipolar Disorder – Severity of Illness (CGI-BP-S)  $\geq 4$ . At any visit, the dose could be reduced to 150 mg/day if the higher dose was not tolerated. The randomized phase of the study was 8 weeks (days 1 – 56) followed by a telephone follow-up visit (day 57 – 63) and a visit for blood pressure measurement if elevations noted at study discontinuation (day 70 – 84).

This study was conducted in 42 centers in 7 countries: the US (29), Columbia (3 centers), India (3 centers), Mexico (2 centers), Serbia (3 centers), South Africa (1 center) and Taiwan (1 center). Approximately 83% (161/193) of subjects randomized were from the United States.

A total of 262 subjects were enrolled into the study, 193 subjects were randomized to receive either quetiapine XR (150 – 300 mg/day) or placebo. One subject randomized to the quetiapine XR group did not receive study medication and did not have a post-baseline CDRS-R assessment; therefore the intent-to-treat (ITT) population included 192 subjects (92 quetiapine XR, 100 placebo). Over 70% completed the study; 49 subjects discontinued the study: 23 in the quetiapine group and 26 in the placebo-treated groups. The common reason for discontinuation included adverse events, lost to follow up, withdrawal of consent, and lack of efficacy.

Patients enrolled were between the ages of 10 and 17 years old with a mean age of 14 years with a higher percentage of patients (72%) in the 13-17 yr group. There were 97 males (50.5%) and 95 females. Approximately 65% were Caucasians, 18% were African Americans and 5% were Asians in this study. Mean body weight and BMI were 64.5 kg and 24.4, respectively. Treatment groups were comparable at baseline on the demographic variables and baseline disease severity, as measured by the CDRS-R (mean total score around 61). Concomitant psychostimulants were allowed for subjects with comorbid ADHD as long as the dose was stable for  $\geq 30$  days prior to randomization. Twenty (22%) subjects in the quetiapine XR group and 28 (28%) subjects in the placebo group took concomitant psychostimulants during the trial.

Efficacy assessments included the CDRS-R and CGI-BP-S. The primary efficacy variable was change from baseline at endpoint (Day 57) on the CDRS-R total score. The primary efficacy analysis was performed using a MMRM model for the ITT population under the assumption of an unstructured covariance matrix. The model included baseline CDRS-R total score as covariate; age stratum, treatment group, time point, and treatment group by time point interaction as fixed effects; and centers and patients within treatment group as random effects.

Our statistical reviewer has confirmed the sponsor's primary efficacy result. Sensitivity analyses were also performed.

Table 1 – Primary Analysis: Change from baseline to endpoint CDRS-R total score in the ITT population (MMRM)

Treatment Groups	Mean Baseline Total Score	LS Mean Change (SE)	Difference in mean changes (drug-placebo)	p-value (drug vs. placebo)
Quetiapine 150-300 mg (N=92)	61.6 (9.9)	-29.6 (1.7)	-2.3	0.25
Placebo (N=100)	60.1 (9)	-27.3 (1.6)		

The results did not show the quetiapine group statistically significantly different from the placebo group in the primary efficacy endpoint.

Comment:

Both Drs. Alfaro and Kordzakhia did not consider this study as a positive study for efficacy of quetiapine extended-release in the treatment of bipolar depression in the pediatric population. I agree with them.

## 7.2 Comments on Other Important Efficacy Issues

### 7.3.1 Subgroup Analyses: Clinical Predictors of Response

Exploratory subgroup analyses were conducted to evaluate the treatment effect: rapid versus non-rapid cycling, bipolar I vs. bipolar II disorder, age stratum, with versus without comorbid ADHD (with/without psychostimulants) and United States versus nonUS sites. These analyses also failed to demonstrate a statistically significant difference between the quetiapine XR and placebo groups. Detailed results were presented in both clinical and statistical reviews.

### 7.3.2 Dose Response Relationship

This study was a flexible-dose study. No dose response analysis was performed.

### 7.3.3 Size of Treatment Effect

The primary efficacy analysis failed to demonstrate a statistically significant difference between quetiapine XR and placebo. The placebo response seems to be large (-28.8).

### 7.3.4 Duration of Treatment

There were no pertinent data from adequately designed and well-controlled studies to address the longer-term efficacy in this submission.

### 7.3.5 Secondary Efficacy Variables

No key secondary variable was identified.

## 7.4 Conclusions Regarding Efficacy (b) (4) in Acute Treatment of Bipolar Depression in Pediatric Population

This study failed to demonstrate the efficacy of quetiapine XR in the treatment of pediatric bipolar depression.

## **8.0 SAFETY**

### **8.1 General Safety Considerations**

During the first review cycle, Dr. Alfaro has posed a number of questions to the Sponsor regarding additional safety information or to clarify apparent discrepancies in the clinical study report (CSR). Given the fact that the sponsor identified additional errors in the analysis database, they conducted a comprehensive quality control review of tables and listings. This resubmission included a revised CSR.

Overall, the safety data from study D144AC00001 are consistent with prior clinical studies conducted with quetiapine. There were no new and significant safety findings in this trial that are not currently identified in approved product labeling.

There were no deaths in this clinical trial. Five patients experienced SAEs during this clinical trial, one patient was receiving quetiapine XR (300 mg) and four patients were receiving placebo. The patient receiving quetiapine XR was a 13 yr old black female who experienced agitation beginning on day 42 and continuing for 8 days, study drug was discontinued and the patient required hospitalization. Three (3.3%) patients in the quetiapine XR group and 12 (12%) patients in the placebo group discontinued the study due to adverse events. One of the patients in the quetiapine group experienced three adverse events that led to discontinuation: headache, sedation, increased fatigue.

The mean (SD) number of days of exposure for the 92 patients in the quetiapine group was 48.3 (14.8) equaling 12 patient-years of exposure. The modal dose was 204.9 mg/day in the quetiapine XR group (range 150 – 300 mg/day); the mean dose was 192 mg/day.

### **8.2 Safety Findings and Issues of Particular Interest**

#### **8.2.1 Common and Drug-Related Adverse Reactions**

The approach that we have used to identify the adverse event profile is by identifying the adverse reactions for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). The adverse reactions that are considered common and drug-related in this study included nausea, diarrhea and fatigue.

#### **8.2.2 Metabolic Effects**

The criteria for potentially significant shifts for the lipid profile were not consistent with the definitions we have asked Sponsors to use for this analysis in the pediatric population. Dr. Alfaro reviewed these shift data in the drug group as compared to the placebo: fasting glucose  $\geq 126$ mg/dl (1.3% vs. 0); cholesterol  $\geq 200$  mg/dL (8.4% vs 6%); HDL  $< 40$  mg/dL (20% vs. 15%) LDL  $\geq 130$ mg/dL(2.3% vs 3.5%); and triglyceride  $\geq 150$  mg/dL (27.5% vs. 8.5%).

The mean change from baseline for weight was 1.3 kg in the quetiapine XR group compared to 0.6 kg in the placebo group. Interestingly, the 10 to 12 year old cohort was the cohort where the weight increase was most significant 2.4 kg in the quetiapine XR group compared to no weight gain in the

placebo group. Similar findings were noted in the weight shift (> 7% gain) data (refer to table 25 and 26 in clinical review for details).

### **8.2.3 Prolactin and Thyroid Function Tests**

Dr. Alfaro noted in her review that prolactin and thyroid tests in this study were considered confounded based on the issues related to blood sampling analysis schedule, and concomitant medications, and results were not reviewed.

### **8.2.4 ECG and Vital Signs**

Mean change from baseline in heart rate was an increase of 3.4 bpm in the quetiapine XR group compared to an increase of 0.3 bpm in the placebo group. Mean change from baseline in QTcB was 1.7 ms in the quetiapine XR group compared to -0.7 ms in the placebo group. No subjects were reported to have QTcF  $\geq$ 450 ms.

Potentially clinically significant increase in blood pressure was defined as  $\geq$  20 mmHg increase in supine SBP and  $\geq$  10 mmHg increase in supine DBP. A greater percentage of subjects in the quetiapine XR group was noted to have supine DBP change as compared to placebo (46.7%, 43/92 vs. 36%, 36/100). This change was evident in the 10 to 12 year old cohort; similar pattern was noted with blood pressure shift data. Refer to Tables 30 and 31 in clinical review for detailed results.

### **8.2.5 Extrapyramidal Symptoms (EPS)**

One subject in the quetiapine XR group had “restlessness”, no other EPS-related adverse events were reported. Dr. Alfaro did not identify any adverse events (verbatim term) consistent with EPS in the sponsor’s data files. EPS rating scales did not demonstrate significant mean changes for quetiapine XR compared to placebo.

## **8.3 Conclusion Regarding Safety Data**

Dr. Alfaro re-reviewed safety data tables in the revised CSR submitted. No new safety concerns were identified in this submission.

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

During the filing meeting, the review team discussed and determined not to take it to the PDAC given this submission did not identify any new safety concern.

## **10.0 PEDIATRICS**

In the original NDA submission, the sponsor requested for a pediatric waiver (age 0-9 yrs) and a deferral (age 10-17 yrs). The sponsor has positive efficacy data from acute pediatric study with Seroquel IR in schizophrenia (12-17) and bipolar mania (10-17). In addition to pediatric safety data from these short-term studies, the sponsor has longer-term safety data with IR from pediatric open-label extension study. The sponsor also submitted data from this pediatric (10-17 yr) study in

bipolar depression with seroquel XR, which was conducted as part of post-marketing PREA requirements. The pediatric assessment was discussed with the PeRC on 3/20/13. The PeRC concurred, and determined that the pediatric assessment has been completed.

## **11.0 OTHER RELEVANT REGULATORY ISSUES**

### **11.1 OSI Clinical Site Inspections**


During the first review cycle of this supplement, routine OSI data audit inspections were conducted for two domestic clinical investigator sites: Site #1124 (David Spiegel, MD of the Brighton Research Group LLC in Virginia Beach, VA) and Site #1125 (Nilesh Patel, M.D. Wharton Research Center in Wharton, TX) were selected for the large subject enrollment. Except for some record keeping deficiencies, OSI did not indicate data integrity issues in these two inspected sites.

### **11.2 Other Outstanding Regulatory Issues**

No financial disclosure issue was identified in this NDA supplement.

## **12.0 LABELING**

The Sponsor incorporated safety data from this clinical trial throughout labeling. The Sponsor also proposed to indicate negative results from this bipolar depression study in pediatric use section. Both Seroquel and Seroquel XR product labeling will be further revised to ensure the labeling is in compliance with the PLR. (b) (4)

 The review team is currently working on the labels. After we provide our labeling comments to the sponsor, we will then negotiate final language with them.

## **13.0 RECOMMENDATION/RISK BENEFIT ASSESSMENT**

I recommend the Division take an approval action on this set of NDA supplements after final labeling agreement is reached with the Sponsor.

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NI A KHIN  
03/26/2013