CLINICAL REVIEW - ADDENDUM

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

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1 Recommendations/Risk Benefit Assessment

The Sponsor submitted two pivotal trials to support the following pediatric indications "treatment of schizophrenia in adolescents (13 to 17 years of age)" and "treatment of bipolar I mania in children and adolescents (10 to 17 years of age)".
Several requests for information were pending at the time the clinical review was finalized. This addendum includes a review of this additional data.

1.1 Recommendation on Regulatory Action

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

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

1.2 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

1.3 Recommendations for Postmarket Requirements and Commitments

No recommendations for postmarket requirements or commitments.

2 Additional Requests for Information

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

2.1 Adverse Events - Sedation and Somnolence

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

The Sponsor submitted the following frequencies for the combined adverse event "somnolence and sedation":
Study 112 (schizophrenia): quetiapine 400 mg/day 32.9%, quetiapine 800 mg/day 35.1% and placebo 10.7%. Study 149 (bipolar disorder): quetiapine 400 mg/day 49.5%, quetiapine 600 mg/day 57.1% and placebo (14.4%)
The pooled frequencies for studies 112 and 149: quetiapine 45.0% and placebo 12.7%

2.2 Clinical Sites in Germany

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

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

2.3 Vital Signs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The Sponsor provided a listing of all patients receiving medications classified as antihypertensives. Some patients received medications for akathisia or ADHD that were classified as antihypertensives (e.g. propranolol, atenolol, clonidine). One 14 YOM patient (E0054102) was taking atenolol for hypertension prior to the study and continued throughout the study, though, notably, the dose was increased from 50 mg/day to 200 mg/day with the addition of other concomitant antihypertensives (irbesartan, ramipril, clonidine). Most of these changes in hypertensive medications were made during the open-label extension phase of the study. A listing of vital signs and concomitant antihypertensive medications for this patient is in the Appendix.
Of note, this listing did not include Patient E0240103 who experienced a hypertensive crises and was treated with enalapril (this patient was included in the SAE summary of the NDA).

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

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

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

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

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

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

2.4 Narratives

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

Study 149: Patient E0035208 - Tachycardia, Blood Pressure Increased
The narrative indicates that the patient experienced these adverse events on Day 5 - however, the vital signs listing does not provide vitals obtained on Day 5. Please provide these data and any other additional vital sign readings obtained for this patient.

The Sponsor provided a listing of all vital signs.

Study 150: Patient E0343103 - Pulmonary Hypertension
The narrative indicates that the patient was referred to a pediatric cardiologist. Please provide the consult and pertinent follow-up for this adverse event. Did the event resolve spontaneously after quetiapine was discontinued, did the patient receive any medical treatment for the condition?

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

Study 150: Patient E0240103 - Hypertensive Crisis
It appears that this patient had high blood pressure during the trial (narrative indicates from day 32 - 212) and enalapril is noted as a concomitant medication. Was enalapril initiated during the trial for high blood pressure? Listing 12.2.9.1 does not indicate high blood pressures for the visits included in the listing and the hypertensive crisis value (150/95) is not included in the listing. Please provide all blood pressures obtained for this patient. Did the patient receive any additional treatment for the 150/95 reading? Please provide more clinical details regarding the hemorrhagic rash experienced by this patient.

The Sponsor indicated that enalapril was initiated during Study 150 for high blood pressure. Enalapril was initiated on 9/20/05 for increased blood pressure, the SAE of hypertensive crises occurred on (b) (6) The patient was hospitalized for the event for 5 days. Patient was treated with diazepam and bendazol without recurrence of high blood pressure. Event resolved within one day without interruption of study drug. Medical records were never obtained so additional details, including the relevant vital signs, are unknown.

On 1/17/06, the patient developed a rash on his skin that was negative for rubella antibodies. The hemorrhagic rash was moderate in intensity and nonserious and resolved within a week.

Study 150: Patient E0262101 - Suicide attempt
Please provide details regarding the suicide attempt - there is no information provided in the narrative. It is noted that this patient also experienced neutropenia with an ANC = 0.46 on Day 85. WBCs were obtained on Days 89 and 96 but, remarkably, no ANCs were obtained for these days. The next available ANC is at Day 169 (resolution). If the value of 0.46 is correct, why was this patient not discontinued? Please comment.

The Sponsor did not provide any details regarding the suicide attempt.
The Sponsor did acknowledge that ANCs were not obtained on Days 89 and 96 but did comment that the WBCs were in the normal range.
Since there can sometimes be a disconnect in WBC and ANC – e.g. WBC within normal range with low ANC, these ANC counts should have been obtained in this reviewer's opinion.

Study 150: Patient E0047211 - Syncope
The narrative notes that the patient also experienced the non-serious event "fall (mild intensity and considered related to study medication) Day 1 Day 20". Does this mean that the patient experienced falls from Day 1 to Day 20? Please clarify and provide additional information.

The patient experienced a "fall" sometime between 7/12/06 and 7/31/06 – the Sponsor indicated that this usually occurs when a patient reports the event and cannot remember the exact date of the event. The dates for the event on the CRF reflect one fall that occurred within that timeframe.

2.5 ANC Clarification

Request: Please clarify the absolute neutrophil counts that are sporadically listed in Listing 12.2.8.2.2 (Study 150). On page 919, patient E0026202 had a WBC count of 5.9 with 25% neutrophils which should be an ANC of 1.47. However, it appears that the ANC listed in the appropriate column indicates a value of 0.18. Please clarify.

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

2.6 Rapid-cycling Bipolar Disorder

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

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

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

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

Source: 6/16/09 submission,

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

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

Source: 6/16/09 submission,

2.7 BID vs. TID Dosing

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

A total of 47 (16.6%) of patients received TID dosing in Study 149 and a total of 33 (14.9%) of patients received TID dosing in Study 112.
In general, the frequencies of adverse events were similar between the BID and TID dosing schedules with few exceptions. The following adverse event frequencies were higher with the TID dosing regimen compared to the BID dosing regimen: akathisia, dizziness, dry mouth, fatigue, increased appetite, nasal congestion, nausea, sedation, somnolence and tachycardia (Tables 6 and 7). There were no significant increases in adverse event frequencies in the BID schedule compared to the TID schedule.

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

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

Source: 6/16/09 submission

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

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

Source: 6/16/09 submission

2.8 Prolactin

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

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

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

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

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

Source: 6/16/09 submission

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

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

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

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

Source: 6/16/09 submission

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

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

Source: Original NDA submission

2.10 Ophthalmoscopic Eye Examinations

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

The sponsor submitted a table summarizing the normal to abnormal and abnormal to abnormal eye examination findings. The sponsor also indicated that 2 of these cases (E0024209 and E0024210) were not included in the original NDA submission since the baseline eye examination should have occurred on Day 1 of Study 150 whereas these occurred on Days 5 and 10 respectively. Interesting that these particular cases had signals suggestive of cataract formation after the baseline examination – these cases should have been included in the original NDA submission.

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

Table 11. Normal to Abnormal Ophthalmoscopic Eye Examinations

Subject	Age at Study Entry, Gender	Baseline Exam	Post Baseline Exam	Clinical Findings
E0242110	15 YOF	7/25/06	1/31/07	Spasm of accommodation Induration crystalline lens
E0341195	NA**	9/28/05	3/29/06	Myopia
E0341109	14 YOM	2/20/06	8/24/06	Myopic astigmatism
E0024210*	15 YOF	4/20/06	10/30/06	*Trace subcapsular cataracts - not visually significant*
E0240101	14 YOM	5/11/05	10/25/05	Myopia
E0242113	17 YOM	11/21/06	2/5/07	Myopic astigmatism

Source: 6/16/09 submission and demographic database in NDA submission
* Patient was not included in original NDA summary table for categorical shift in eye examination
** Could not find patient in demographic or other databases, likely an error in subject number in the 6/16 submission

Table 12. Abnormal to Abnormal Ophthalmoscopic Eye Examinations

Subject	Age at Study Entry, Gender	Baseline Exam	Post Baseline Exam	Clinical Findings
E0024209*	15 YOF	4/10/06	10/25/06	*Baseline - myopia* *Post BL - Pinpoint cataracts both eyes – suggestive of congenital abnormality. Visually insignificant.*
E0026203	13 YOF	10/28/04	1/13/05	Both exams same finding – right eye cortical focal opacity
E0028208	13 YOM	2/21/05	8/25/05	*Both exams same finding – ocular lenses showed punctuate opacities – a few in the right lens and fewer in the left lens*
E0220105	14 YOM	3/29/07	9/26/07	Both exams same finding – myopia
E0240108	16 YOF	6/13/06	12/12/06	Both exams same finding – myopia
E0241104	16 YOM	12/6/05	6/29/06	Both exams same finding – astigmatism
E0241105	17 YOM	5/26/06	11/28/06	Both exams same finding – myopic astigmatism and myopia
E0241106	16 YOM	5/15/06	11/21/06	Baseline – astigmatism Post BL – myopic astigmatism
E0241107	17 YOF	5/26/06	11/28/06	Both exams same finding – myopia
E0241108	17 YOM	6/14/07	11/28/05	Both exams same finding – myopia
E0242103	17 YOM	11/21/05	5/29/06	Both exams same finding – myopic astigmatism
E0242107	17 YOF	3/27/06	10/04/06	Both exams same finding – myopic astigmatism
E0242112	16 YOM	11/15/06	5/24/07	Both exams same finding – myopic astigmatism and myopia
E0242115	17 YOM	1/31/07	8/7/07	Abnormalities not specified
E0243101	15 YOF	5/7/07	11/6/07	Both exams same finding – myopia and angyopathia
E0341102	17 YOM	4/27/05	10/28/05	Both exams same finding – pterygium nasal left eye
E0341106	16 YOF	11/17/05	5/19/06	Both exams same finding – myopic astigmatism
E0341112	17 YOM	5/7/07	11/7/07	Both exams same finding – corneal macula, right eye secondary to trauma; myopic astigmatism

Source: 6/16/09 submission and demographic database in NDA submission
* Patient was not included in original NDA summary table for categorical shift in eye examination

2.11 Vital Signs: Concomitant Psychostimulants

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

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

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

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

Source: 6/16/09 submission

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

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

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

Source: 6/16/09 submission

3 Labeling

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

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

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

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

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

Increases in Blood Pressure (Children and Adolescents)
In proposed labeling, hypertension (an adverse event occurring specifically in this population) is listed as the 14th item in this section. I propose moving this up higher in the list, perhaps following orthostatic hypotension (listed 8th) since it is a vital signs related significant adverse event. Also recommend inclusion of the one case of hypertensive crises occurring in the open label trial as this adverse event was significant enough to require hospitalization as well as continued treatment with antihypertensives.

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

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

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

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

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

(b) (4)

4 Appendices

4.1 Vital Signs Listings for Select Patients

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

Quetiapine	EE0054102 14 YOM			
	SBP	DBP	Pulse	Antihypertensive
Day -7	130	80	80	atenolol 50 mg/d
Day 1	120	70	70	atenolol 50 mg/d
Day 8	115	70	70	atenolol 50 mg/d
Day 15	120	70	80	day 12: increase to atenolol 100 mg/d
Day 22	120	70	85	
Day 28	130	80	84	
Day 36	140	70	92	
Day 43	120	80	78	
OL Week 1	140	60	88	
OL Week 2	120	70	85	
OL Week 3	125	70	78	
OL Week 4	120	80	84	
OL Week 8	130	80	85	Increase to atenolol 200 mg/d, added ramipril
OL Week 12	120	80	80	
OL Week 16	115	70	70	Added irbesartan
OL Week 20	115	70	90	
OL Week 26	120	80	82	

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

Quetiapine	EE0024102 15 YOM		
	SBP	DBP	Pulse
Day -2	129	59	59
Day 1	137	65	66
Day 7	**165**	76	85
Day 14	132	67	88
Day 21	121	63	91
Day 28	133	65	92
Day 36	142	71	107
Day 43	117	54	80

Quetiapine	EE0041102 17 YOM		
	SBP	DBP	Pulse
Day -5	122	64	84
Day 1	136	66	78
Day 8	138	72	67
Day 16	120	76	78
Day 22	120	72	78
Day 29	118	70	72
Day 36	120	68	76
Day 43	**151**	69	88

Quetiapine	EE0320101 17 YOM		
	SBP	DBP	Pulse
Day -11	132	72	95
Day 1	135	66	89
Day 9	146	76	102
Day 15	143	70	86
Day 25	120	90	90
Day 35	131	73	108
Day 45	133	58	111
Day 51	**159**	82	90

Quetiapine	EE0024212 14 YOM		
	SBP	DBP	Pulse
Day -9	131	75	90
Day 1	134	75	94
Day 9	137	73	105
Day ?	**152**	88	111
Day 14	142	81	97
Day 23	140	72	98

Placebo	EE0041104 14 YOM		
	SBP	DBP	Pulse
Day -4	139	66	65
Day 1	131	70	98
Day 7	135	57	85
Day 14	142	58	73
Day 19	133	75	72
Day 26	**163**	64	64
Day 34	107	57	78
Day 43	135	66	59

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

Quetiapine	E0261106 15 YOM		
	SBP	DBP	Pulse
Day -22	105	65	84
Day -9	105	65	84
Day 1	110	65	88
Day 9	110	70	84
Day 16	110	65	84
Day 23	120	70	82
Day 30	140	**100**	96
Day 37	130	**90**	88
Day 43	130	**110**	86

Quetiapine	E0261108 17 YOM		
	SBP	DBP	Pulse
Day -12	130	95	78
Day 1	120	80	76
Day 8	130	90	100
Day 15	150	90	86
Day 22	150	90	96
Day 29	140	90	104
Day 37	140	90	84
Day 43	140	100	86

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

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/s/

CARA L ALFARO
08/11/2009

NI A KHIN
08/13/2009
I concur with Dr. Alfaro's recommendation that this set of NDA supplements be considered for approval; see memo to file for additional comments.