DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDAs 20-639, 22-047

Gerald Limp
Director, Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) Tablets (NDA 20-639) and Seroquel XR (quetiapine fumarate) Extended-Release Tablets (NDA 22-047).

The Division of Psychiatry Products is evaluating the effects of atypical antipsychotic drugs on metabolic parameters (e.g., weight, lipids, and glucose). We are writing to request analyses from your clinical development program.

Subject Groups to Be Evaluated

In Table 1 below, we outline the subject groups for which we request information. For each analysis discussed subsequently, we request evaluation related to each of the groupings in Table 1 (9 total), unless otherwise noted.

Table 1. Subject Groups to Be Evaluated

I. All Adult Subjects
   1. Adult Subjects in Placebo-Controlled Trials
   2. Adult Subjects in Comparator-Controlled Trials §
   3. All Adult Quetiapine-treated Subject Data, Controlled and Uncontrolled

II. Pediatric and Adolescent Subjects (Age <18 at Time of Enrollment) †
   1. Pediatric and Adolescent Subjects in Placebo-Controlled Trials
   2. Pediatric and Adolescent Subjects in Comparator-Controlled Trials §
   3. All Pediatric and Adolescent Quetiapine-treated Subject Data, Controlled and Uncontrolled

III. Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects*
   1. Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects in Placebo-Controlled Trials
   2. Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects in Comparator-Controlled Trials §

3. All Data for Quetiapine-treated Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects, Controlled and Uncontrolled

§ For evaluations of comparator-controlled trials, we request separate evaluations for each comparator with data for more than 50 subjects.

† Include all pediatric and adolescent subjects, including subjects in trials that do not enroll only pediatric or adolescent subjects.

* This subject group is comprised of two categories of subjects: subjects with first episode psychosis and antipsychotic-naïve subjects. This group includes subjects from trials with psychiatric indications only and includes adult and pediatric subjects. Include all subjects with first episode psychosis and all antipsychotic-naïve subjects, including subjects in trials that did not enroll these types of subjects exclusively. We define antipsychotic-naïve subjects as those who have received antipsychotic therapy for four months or less prior to study enrollment.

Subject Exclusion Criteria

We request the exclusion of subjects from trials that meet the following criteria:

- Studies without a source drug monotherapy arm
- Studies with duration under 7 days
- Studies with a relapse-prevention study design, in which subjects had source drug exposure prior to randomization
- Studies evaluating the source drug using routes of drug delivery other than oral drug delivery (e.g., intramuscular, intravenous)

Tables Summarizing Clinical Trials for Each Subject Group

We request tables with summary information on clinical trials with metabolic data. For each subject group in Table 1 (9 total) provide a data table with the 18 columns summarized in Table 2. Each row should contain information on a single clinical trial.

Table 2. Clinical Trial Information

Column Number	Column Name	Description	Notes
1	Study	Clinical Trial Name	
2	Indication	Trial Indication	

Column Number	Column Name	Description	Notes
3	Quetiapine N	Number of subjects in the clinical trial who received the source drug	
4	Quetiapine Dose Range	Range of source drug doses used in the clinical trial	
5	Placebo N	Number of subjects in the clinical trial who received placebo. If no subjects received placebo, leave the column blank.	
6	Comparator	Name of the comparator(s) used in the trial. Multiple comparators may be listed.	
7	Comparator N	Number of subjects in the trial who received the comparator. If there are multiple comparators, list comparator N adjacent to the comparator (see example).	<table><tr><td>Comparator</td><td>Comparator N</td></tr><tr><td>Comp 1 Comp 2</td><td>43 55</td></tr></table>
8	Total Cholesterol	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
9	HDL Cholesterol	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
10	LDL Cholesterol	If not measured, leave blank. Otherwise, enter one of the following:	

Column Number	Column Name	Description	Notes
		R (random) NF (non-fasting) F (fasting	
11	Triglycerides	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
12	Glucose	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
13	HbA1c	Hemoglobin A1c. If not measured, leave blank. If measured, enter Y for yes.	
14	UA glucose	Urine glucose. If not measured, leave blank. If measured, enter Y for yes.	
15	Weight	If not measured, leave blank. If measured, enter Y for yes.	
16	Duration Controlled	Enter the duration controlled in weeks.	
17	Duration Uncontrolled	Enter the Duration Uncontrolled in Weeks	
18	Notes	Any additional notes about the study (optional).	

Tables Summarizing Subject Demographic Information

We request demographic tables for each of the nine subject groups described in Table 1 with the following information:

- Mean Age
- Gender
- Race
- Treatment Indication
- Mean Modal Dose Received
- Median Time of Exposure to Treatment
- Number of Years Since First Antipsychotic Medication Prescribed (if available)
- Percent Discontinued due to Lack of Efficacy
- Percent Discontinued to Side Effect
- Percent Discontinued Due to Metabolic Side Effect
- Mean Baseline Weight
- Mean Baseline BMI

Tables Summarizing Subject Metabolic Data

Each data table should clearly list:

- The studies from which analyses were derived
- The mean modal dose of treatment received by each subject group
- The median, range, and interquartile range of treatment exposure time for each subject group

We have the following specific requests regarding the analysis plan for weight, lipids, and glucose:

I. Weight

I. A. Weight: Mean Change Analyses

- We request analyses of simple mean changes in weight and in body mass index (BMI) from baseline to last observation carried forward (LOCF) endpoint for all patients in each subject group; we also request similar mean change analyses of subgroups divided according to World Health Organization categories of baseline BMI: Underweight (BMI<18.5), Normal Weight (18.5≤BMI<25), Overweight (25≤BMI<30), and Obese (BMI≥30). We request that treatment effect be assessed based on an analysis of variance (ANOVA) model with terms for protocol and treatment. It is not necessary to perform this analysis on the combined controlled and uncontrolled subject groups.

- We request observed case analyses of mean change for the following specified exposure durations: 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks. For these analyses, mean weight change should be reported for all patients who completed the study time up to the time point specified for that analysis. Comparison between treatment groups should be conducted and p-values reported. We request information on all subject groups in Table 1 for this analysis.

I. B. Weight: Categorical Analyses

To assess for weight gain outliers in each subject group, stratifying by treatment exposure time, we request analyses similar in format to the table below:

Table 3. Combined Weight Data

	6 weeks		6 months		12 months		24 months		36 months	
Weight change (kg)	n	%	n	%	n	%	n	%	n	%
Wt change ≤0	500	10								
0<Wt change≤5	500	10								
5<Wt change≤10	500	10								
10<Wt change≤15	500	10								
15<Wt change≤20	500	10								
20<Wt change≤25	500	10								
25<Wt	500	10								

change≤30										
30<Wt change≤35	500	10								
35<Wt change≤40	500	10								
Wt change>40	500	10								
Total for time point	5000	100		100		100		100		100

- Using this format, we request analyses for all subject groups in Table 1.
- Since changes in weight are sometimes difficult to interpret in pediatric populations, we request additional tables displaying change in BMI. The format is similar to Table 3, except that it substitutes "BMI Change" for "Weight Change." The BMI change categories should be as follows: BMI change ≤0, 0<BMI change≤1, 1<BMI change≤2, 2<BMI change≤3, 3<BMI change≤4, 4<BMI change≤5, 5<BMI change≤6, 6<BMI change≤9, 9<BMI change≤12, 12<BMI change≤15, and BMI change>15.
- Please ensure that analyses have not included individual subjects more than once.

II. Lipids

II. A. Lipids: Mean Change Analyses

- Assess simple mean changes in the following lipid parameters: total cholesterol (combined fasting and non-fasting), fasting triglycerides, non-fasting triglycerides, HDL cholesterol (combined fasting and non-lasting), and fasting LDL cholesterol. We request that treatment effect be assessed based on an analysis of variance (ANOVA) model with terms for protocol and treatment. It is not necessary to perform this analysis on the combined controlled and uncontrolled subject groups. Otherwise, we request analyses for the placebo-controlled and comparator-controlled subject groups in Table 1.
- We request analyses of all subject groups listed in Table 1. Because exposure time is essential to interpreting lipid results, we request for each subject group separate analyses of: 1.) All subjects and 2.) Subjects with at least 12 weeks of exposure 3.) Subjects with at least 24 weeks of exposure.
- We request that median exposure at time of lipid measurement also be listed with each table related to lipids. This is in addition to information on clinical trials included in calculations, drug exposure time, and dose requested earlier in this document.
- Report the mean baseline lipid value, post-treatment lipid value, and magnitude of change.

II. B. Lipids: Categorical Analyses

II. B. 1. Lipid Categorical Analyses: Adult Subjects

- We request analyses of all subject groups listed in Table 1. Because exposure time is essential to interpreting lipid results, we request for each subject group in Table 1 separate analyses of: 1.) All subjects and 2.) Subjects with at least 12 weeks of exposure 3.) Subjects with at least 24 weeks of exposure.
- We request that median exposure at time of lipid measurement also be listed with each table related to lipids. This is in addition to information previously requested on studies included, dose, and treatment exposure time.
- In tables of categorical lipid analyses, report the mean or median baseline, post-baseline, and change in lipid values for each analysis.
- We request the following analyses of treatment-emergent significant changes in lipids listed in Tables 4 and 5.

Table 4. Treatment-Emergent Significant Changes in Lipids: Based on NCEP-based Classifications for Adults*

	Baseline	Postbaseline
Total Cholesterol (Fasting and Non-Fasting)*		
Normal to High	<200 mg/dL	≥240 mg/dL
Borderline to High	≥200 and <240 mg/dL	≥240 mg/dL
Normal/Borderline to High	<240 mg/dL	≥240 mg/dL
Normal to Borderline/High	<200 mg/dL	≥200 mg/dL
LDL Cholesterol (Fasting)		
Normal to High	<100 mg/dL	≥160 mg/dL
Borderline to High	≥100 and <160 mg/dL	≥160 mg/dL
Normal/Borderline to High	<160 mg/dL	≥160 mg/dL
Normal to Borderline/High	<100 mg/dL	≥100 mg/dL
HDL Cholesterol (Fasting and Non-fasting)*		
Normal to Low	≥40 mg/dL	<40 mg/dL
Triglycerides (Fasting)		
Normal to High	<150 mg/dL	≥200 mg/dL
Normal to Very High	<150 mg/dL	≥500 mg/dL
Borderline to High	≥150 and <200 mg/dL	≥200 mg/dL
Borderline to Very High	≥150 and <200 mg/dL	≥500 mg/dL
Normal/Borderline to High	<200 mg/dL	≥200 mg/dL
Normal/Borderline to Very High	<200 mg/dL	≥500 mg/dL

Normal to Borderline/High/Very High	<150 mg/dL	≥150 mg/dL

* The National Cholesterol Education Program (NCEP) Adult Treatment Program Classifications of lipids refer to fasting lipid measurements. However, given that total cholesterol and HDL cholesterol measurements are not significantly changed by fasting status and that the majority of clinical trial lipid data is non-fasting, we elect to include fasting and non-fasting values for total cholesterol and HDL cholesterol in combined analyses.

Table 5. Treatment-Emergent Significant Changes in Lipids: Additional Analyses

	Baseline	Post-baseline
Treatment- emergent very high triglycerides (fasting)	Fasting triglycerides <500 mg/dL	Fasting triglycerides ≥500 mg/dL
Treatment-emergent very high triglycerides (non-fasting and random)	Non-fasting and random triglycerides <500 mg/dL	Non-fasting and random triglycerides ≥500 mg/dL
Treatment-emergent triglycerides >1000 mg/dL (All cases—fasting, non-fasting, and random)	Triglycerides <1000 mg/dL	Triglycerides ≥1000 mg/dL
Change in fasting or non-fasting total cholesterol ≥40 mg/dL at any time post-baseline[1]	Any value	Increased fasting or non-fasting total cholesterol ≥40 mg/dL
Change in fasting LDL cholesterol ≥ 30 mg/dL at any time post-baseline[2]	Any value	Increased fasting LDL cholesterol ≥ 30 mg/dL
Change in fasting or non-fasting HDL cholesterol ≥20 mg/dL at any time post-baseline[3]	Any value	Decreased fasting or non-fasting HDL cholesterol ≥20 mg/dL
Change in fasting triglycerides ≥50 mg/dL at any time post-baseline[4]	Any value	Increased fasting triglycerides ≥50 mg/dL

[1] We also request subgroup analyses based on the following categories of baseline fasting or nonfasting total cholesterol for adults: Normal (<200 mg/dL), Borderline (≥200 and <240 mg/dL), and High (≥240 mg/dL). For pediatric subjects use the total cholesterol categories listed in Table 6.
[2] We also request subgroup analyses based on the following categories of baseline fasting LDL cholesterol for adults: Normal (<100 mg/dL), Borderline (≥100 and <160 mg/dL), and High (≥160 mg/dL). For pediatric subjects use the fasting LDL cholesterol categories listed in Table 6.
[3] We also request subgroup analyses based on the following categories of baseline fasting or non-fasting HDL cholesterol: Normal (≥40 mg/dL) and Low (<40 mg/dL).
[4] We also request subgroup analyses based on the following categories of baseline fasting triglycerides: Normal (<150 mg/dL), Borderline (≥150 and <200 mg/dL), High (≥200 and <500 mg/dL), and Very High (≥500 mg/dL).

II. B. 2. Lipid Categorical Analyses: Pediatric Subjects

Because the National Cholesterol Education Program (NCEP) defines borderline and high cut-off values for LDL cholesterol and total cholesterol differently in pediatric subjects, we request using these criteria in pediatric subject analyses.[1] The LDL cholesterol criteria apply to fasting lipid measurements, and the total cholesterol criteria apply to fasting and non-fasting lipid measurements.

Since NCEP has designated specific pediatric cut-off values for neither HDL cholesterol nor triglycerides, we request using identical categories for clinically significant changes in HDL cholesterol and triglycerides in adult and pediatric subjects (see Tables 4 and 5 above).

Regarding the pediatric and adolescent subject groups only, we request the following categorical lipid analyses (Tables 7) based on the NCEP criteria (Table 6).

Table 6. Criteria for Abnormal Metabolic Values in Pediatric Subjects

Criterion	Abnormal Value in Pediatric Subjects
Normal Fasting LDL Cholesterol Level	<110 mg/dL
Borderline Fasting LDL Cholesterol Level	110-129 mg/dL
High Fasting LDL Cholesterol Level	≥130 mg/dL

[1] NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents. National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 1992; 89(3):495-501.

Normal Total Cholesterol Level	<170 mg/dL
Borderline Total Cholesterol Level	170-199 mg/dL
High Total Cholesterol Level	≥200 mg/dL

Table 7. Pediatric Categorical Analyses: Treatment-Emergent Significant Changes in Lipids

	Baseline	Post-baseline
Normal to borderline total cholesterol level (fasting and non-fasting values)	<170 mg/dL	170-199 mg/dL
Normal to high total cholesterol level (fasting and non-fasting values)	<170 mg/dL	≥200 mg/dL
Borderline to high total cholesterol levels	170-199 mg/dL	≥200 mg/dL
Normal to borderline fasting LDL cholesterol level	<110 mg/dL	110-129 mg/dL
Normal to high fasting LDL cholesterol level	<110 mg/dL	≥130 mg/dL
Borderline to high fasting LDL cholesterol level	110-129 mg/dL	≥130 mg/dL

III. Glucose

III. A. Glucose: Mean Change Analyses

III. A. 1. Glucose: Overall Mean Change Analyses

We request analysis of mean and median changes in serum glucose levels from baseline to endpoint (separate analyses for fasting and non-fasting data). We also request mean and median changes in serum glucose levels from baseline to highest measurement (separate analyses for fasting and non-fasting data).

We also request observed case analyses of mean change for the following specified exposure durations: 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks. For these analyses, mean change in serum glucose from baseline to highest post-baseline measurement should be reported for all subjects who completed the study time up to the time point specified for that analysis. Comparison between treatment groups should be conducted and p-values reported. We request information on all subject groups in Table 1 for this analysis.

III.A. 2. Glucose: Mean Change Analyses by Baseline Values

We request that each of the mean change analyses (baseline to endpoint and baseline to highest measurement for fasting and non-fasting data) described in section III.A.1 also be performed with stratification according to baseline serum glucose measurement for each of the six categories in Table 8, as follows:

Table 8. Categorization of Serum Glucose Levels (Based on American Diabetes Association Criteria)

Fasting Serum Glucose	
Normal	<100 mg/dL
Impaired Fasting Glucose	100-125 mg/dL
Diabetes (High)	≥126 mg/dL
Non-fasting Serum Glucose	
Normal	<140 mg/dL
Borderline	140-199 mg/dL
High	≥200 mg/dL

III. B. Glucose: Categorical Analyses

We request analyses of proportions of subjects with treatment-emergent changes of interest at any time post-baseline as described in Table 9 below. We request that you compare the proportions of subjects with clinically significant changes using Fisher's exact test.

Table 9. Serum Glucose: Criteria for Clinically Significant Changes

	Baseline	Post-Treatment
Fasting Serum Glucose		
Normal to High	<100 mg/dL	≥126 mg/dL
Impaired Fasting Glucose to High	100-125 mg/dL	≥126 mg/dL
Normal/Impaired Fasting Glucose to High	<126 mg/dL	≥126 mg/dL
Change in fasting serum glucose ≥10 mg/dL at any time post-baseline*	Any value	Fasting glucose increased ≥10 mg/dL
Non-Fasting Serum Glucose		
Normal to High	<140 mg/dL	≥200 mg/dL
Borderline to High	140-199 mg/dL	≥200 mg/dL
Normal to Borderline/High	<140 mg/dL	≥140 mg/dL
Normal/Borderline to High	<200 mg/dL	≥200 mg/dL
Change in non-fasting serum glucose ≥20 mg/dL at any time post-baseline*	Any value	Non-fasting glucose increased ≥20 mg/dL

* For these two analyses, we request additional subgroup analyses divided according to baseline glucose levels. Please use the categorizations of fasting serum glucose and non-fasting serum glucose listed in Table 8 to define the subgroups.

In addition to the analyses listed in Table 9, we request similar analyses using the following additional serum glucose cut-off values:

- For fasting serum glucose, we request analyses of the proportion of subjects with post-treatment levels of 140 mg/dL, 200 mg/dL, and 300 mg/dL.
- For non-fasting glucose, we request analyses of the proportion of subjects with post-treatment level of 300 mg/dL.

We request analyses of the proportion of subjects with post-baseline hemoglobin A1c $\geq$ 6.1%,[2] 8%, 10%, and 12% among patients with baseline hemoglobin A1c values below 6.1%.

We also request analyses of the proportion of subjects with treatment-emergent glycosuria (defined as any glucose in the urine) for each subject database listed in Table 1.

Time Frame for Submission to the Division of Psychiatry Products

Responses to this information request may be submitted in stages. Specifically, information from placebo-controlled trials (all subject groups), comparator-controlled trials (all subjects groups), and combined controlled and uncontrolled data (all subjects), may be submitted separately, as they are completed. We expect that the response to all components of this request will be submitted by June 30, 2008.

If you have any questions, call Sonny Saini, Pharm.D., Safety Regulatory Project Manager, at (301) 796-0532.

Sincerely,
{See appended electronic signature page}
Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

[2] Rohlfing, CL, Little RR, Wiedmeyer, HM, et al. Use of GHb (HbA(1c)) in screening for undiagnosed diabetes in the U.S. population; Diabetes Care 2000: 23(2), 187-191.

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/s/

Thomas Laughren
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