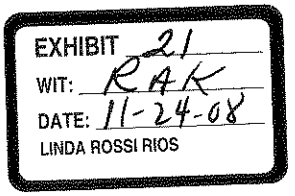
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-639/S-036
NDA 22-047/S-001



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

Dear Mr. Limp:

We acknowledge receipt of your supplemental new drug applications dated June 22, 2007, and July 25, 2007, 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).

We additionally refer to an Agency letter dated January 8, 2008, requesting information on glucose abnormalities.

These applications, submitted as "Changes Being Effected" supplements, provide for the following revisions to product labeling:

20-639/S-036 dated June 22, 2007

- Revisions throughout labeling to provide for new information on quetiapine and hyperglycemia.

22-047/S-001 dated July 25, 2007

- Revisions throughout labeling to provide for new information on quetiapine and hyperglycemia.
- Revisions to the **Adverse Reactions**-Postmarketing Experience section.
- Revisions to the **Drug Interactions**-P450 3A Inhibitors section.

We have completed our review of these supplemental applications, and they are approvable.

In general, the revisions made to the Postmarketing Experience and Drug Interactions sections are acceptable, and these comments were conveyed to you in an Agency letter dated May 13, 2008.

However, we are requesting the following changes to your proposed labeling (double underline font denotes additions and strike through font denotes deletions) before we can take a final action on these supplemental applications.

> *In 2 long-term placebo-controlled randomized withdrawal clinical trials, mean exposure of 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dl) ~~for patients more than 8 hours since a meal~~ was 18.0 per 100 patient years for SEROQUEL (10.7% of patients)*

and 9.5 for placebo per 100 patient years (4.6% of patients). The mean change in glucose from baseline was +5.0 mg/dl for SEROQUEL and -0.05 mg/dl for placebo. Because of limitations in the study design of these long-term trials as well as lack of confirmed fasting glucose data, the effects of SEROQUEL on blood glucose may be underestimated.

For the 2 long term placebo-controlled bipolar maintenance trials, we are deleting the statement "more than 8 hours since a meal" from the proposed labeling language. In general, it does indicate fasting, but you indicated that there was still the possibility of caloric intake in the form of liquids or snacks. Therefore, since these subjects may not have been in a fasting state, this phrase should be deleted to reduce confusion.

Since the 2 long-term placebo-controlled bipolar maintenance trials studies were randomized withdrawal trials, there is some bias in that only subjects who were able to tolerate quetiapine in the open-label phase are then randomized. If subjects did not tolerate quetiapine in the open label phase, if they dropped out due to elevations in blood glucose for example, they would not be randomized and the overall effect of the drug on this parameter would be skewed. Therefore, because of this design issue, the overall effect of Seroquel on blood glucose could be underestimated.

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 treated with Seroquel and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl was 3.5% for quetiapine and 2.1% for placebo. The mean increase in glucose from baseline was 2.70 mg/dl for SEROQUEL and 1.06 mg/dl for placebo.

For the 24 week active-controlled trial designed to evaluate glycemic status, you included only the LS mean data, and not the mean change from baseline to week 24 for the quetiapine group. Please provide us these data so that it can be incorporated into product labeling.

Based on the PLR regulations, your proposed addition of "Adverse Reactions, Vital Signs and Laboratory Studies, Hyperglycemia (6.2)" under RECENT MAJOR CHANGES in the Highlights should be deleted.

Additionally, we would refer you to our January 8, 2008 letter requesting information on the following glucose data. Please submit these information by the requested due date, June 30, 2008.

- Glucose mean and median change analyses of serum glucose levels by baseline values (baseline to endpoint and baseline to highest measurement for fasting and non-fasting data)
- Fasting serum glucose post-treatment cut-off values are 140 mg/dL, 200 mg/dL, and 300 mg/dL
- Non-fasting serum glucose post-treatment cut-off value level is 300 mg/dL
- Observed case analyses of mean glucose change for the following specified exposure durations - 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks
- Analyses of the proportion of subjects with post-baseline hemoglobin A1c ≥ 6.1%, 8%, 10%, and 12% among patients with baseline hemoglobin A1c values below 6.1%

- Analyses of the proportion of subjects with treatment-emergent glycosuria (defined as any glucose in the urine) for each subject

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at 301-796-2201.

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

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

/s/

Thomas Laughren
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