DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21590/S-024

SUPPLEMENT APPROVAL

Azur Pharma
C/O Beckloff Associates
Attention: Gary D. Hindman, PhD, MBA
Director, Managing Consultant
7400 W. 110th Street, Suite 300
Overland Park, KS 66210

Dear Dr. Hindman:

Please refer to your Supplemental New Drug Application (sNDA) dated December 2, 2011, received December 5, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fazaclo (clozapine) Orally Disintegrating Tablets, 12.5 mg, 25 mg, 100 mg, 150 mg, and 200 mg.

This "Prior Approval" supplemental new drug application proposes the following additions of QT interval prolongation language as requested in the Agency's prior approval supplement request letter dated November 2, 2011:

[Double underline font denotes additions to the labeling.]

Under Warnings:

Prompt discontinuation of FazazClo® (clozapine, USP) treatment is warranted upon suspicion of myocarditis. Patients with clozapine-related myocarditis should not be rechallenged with FazaClo® (clozapine, USP) .

QT Interval Prolongation
QT prolongation is associated with an increased risk for life-threatening ventricular arrhythmias including Torsades de Pointes. Treatment with FazaClo® (clozapine, USP) , has been associated with QT prolongation as well as ventricular arrthymia, Torsades de Pointes, cardiac arrest, and sudden death.
Caution should be exercised when FazaClo® (clozapine, USP) is prescribed in patients with a history of long QT syndrome or QT prolongation, or other conditions that may increase their risk for QT prolongation or sudden death, including recent acute myocardial infarction, uncompensated heart failure, or clinically significant cardiac arrhythmia.
Caution is also indicated when treating patients with cardiovascular disease or family history of long QT syndrome.
Caution should be exercised when FazaClo® (clozapine, USP) is used in combination with other medications known to prolong the QTc interval. These include certain antipsychotic

medication (e.g., ziprasidone, iloperidone, chlorpromazine, thioridazine, mesoridazine, droperidol, pimozide), certain antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin), antiarrhythmic medication in Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol), and other medications known to prolong the QT interval (e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol or tacrolimus) (see DRUG INTERACTIONS).
Hypokalemia, (which can result from diuretic therapy, diarrhea, and other causes), and/or hypomagnesemia can also increase the risk of QT prolongation. Use caution when treating patients at risk for significant electrolyte disturbance, particularly hypokalemia. Baseline measurements of serum potassium and magnesium levels, as well as periodic monitoring of electrolytes, should be performed. Electrolyte abnormalities should be corrected before initiating treatment with FazaClo® (clozapine, USP) .
Persistent QT prolongation predisposes patients to further QTc prolongation and potentially to significant and life-threatening cardiac arrhythmias. Routine ECG assessment may detect QTc prolongation but is not always effective in preventing arrhythmias. FazaClo® (clozapine, USP) treatment should be discontinued if the QTc interval exceeds 500 msec. Patients taking FazaClo® (clozapine, USP) who experience symptoms that could indicate the occurrence of Torsades de Pointes, (e.g., syncope, dizziness and palpitations) should have further evaluation, including cardiac monitoring.

Use caution when prescribing FazaClo® (clozapine, USP) concomitantly with drugs that inhibit the metabolism of FazaClo® (clozapine, USP) . FazaClo® (clozapine, USP) is primarily metabolized by CYP isoenzymes 1A2, 2D6, and 3A4. Use caution when prescribing FazaClo® (clozapine, USP) in patients with reduced activity of 1A2, 2D6, and 3A4 (see DRUG INTERACTIONS AND CLINICAL PHARMACOLOGY).

Under Drugs Interactions and Pharmacodynamic-Related Interactions:

FAZACLO® (CLOZAPINE, USP) may potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

QT prolongation: Treatment with FazaClo® (clozapine, USP) , has been associated with QT interval prolongation and fatal arrhythmia. FazaClo® (clozapine, USP) should be used with caution when co-administered with medications known to prolong the QTc interval. Such medications include: Class 1A (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrrythmic medications, certain antipsychotic medications (e.g., ziprasidone, iloperidone, chlorpromazine, thioridazine, mesoridazine, droperidol, pimozide), certain antibiotics (e.g. gatifloxacin, moxifloxacin, sparfloxacin), and other medications known to prolong the QT interval (e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol and tacrolimus). Use caution when co-administering FazaClo® (clozapine, USP) with medications that can cause electrolyte imbalance (e.g., diuretics) **[see WARNINGS].**

Pharmacokinetic-Related Interactions

Clozapine is a substrate for many CYP450 isozymes, in particular 1A2, 2D6, and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimized. Nevertheless, caution should be used in patients receiving concomitant treatment with other drugs that are either inhibitors or inducers of these enzymes.

Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine. Phenytoin, tobacco smoke, and rifampin may decrease FazaClo® (clozapine, USP) plasma levels, resulting in a decrease in effectiveness of a previously effective FazaClo® (clozapine, USP) dose.

QT Prolongation: Use caution when prescribing FazaClo® (clozapine, USP) concomitantly with drugs that inhibit FazaClo® (clozapine, USP) metabolism. FazaClo® (clozapine, USP) is primarily metabolized by CYP isoenzymes 1A2, 2D6, and 3A4. Use caution when prescribing FazaClo® (clozapine, USP) in patients with reduced activity 1A2, 2D6, and 3A4.

Under Postmarketing Clinical Experience:

Cardiovascular System: atrial or ventricular fibrillation and periorbital edema.

Ventricular tachycardia, cardiac arrest, QT prolongation, and Torsades de Pointes.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, email Ann Sohn, Regulatory Project Manager, at ann.sohn@fda.hhs.gov

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

ENCLOSURE:
Content of Labeling

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

/s/

THOMAS P LAUGHREN
01/09/2012