DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21590/S-017 **SUPPLEMENT APPROVAL**

Azur Pharma International III Limited
Attention: Gary D. Hindman, Ph.D., M.B.A., U.S. Agent
Beckloff Associates, Inc.
Regulatory Affairs
7400 W. 110th Street, Suite 300
Overland Park, KS 66210

Dear Dr. Hindman:

Please refer to your Supplemental New Drug Application (sNDA) dated August 13, 2010, received August 16, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fazaclo (clozapine) orally disintegrating tablets.

Reference is also made to an Agency letter dated July 13, 2010, requesting revisions to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections of Fazaclo labeling.

This "Prior Approval" supplemental new drug application proposes the following changes as requested in our letter dated July 13, 2010:

PRECAUTIONS

Interference with Cognitive and Motor Performance

Because of initial sedation, FAZACLO may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness.

Cerebrovascular adverse events

An increased risk of cerebrovascular adverse events has been seen in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Fazaclo should be used with caution in patients with risk factors for stroke.

Use in Patients with Concomitant Illness

Clinical experience with FAZACLO in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using FAZACLO in patients with renal or cardiac disease.

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, ~~nicotine~~ tobacco smoke, and rifampin may decrease FAZACLO plasma levels, resulting in a decrease in effectiveness of a previously effective FAZACLO dose.

Postmarketing Clinical Experience
Postmarketing experience has shown an adverse experience profile similar to that presented above. Voluntary reports of adverse events temporally associated with clozapine not mentioned above that have been received since market introduction and that may have no causal relationship with the drug include the following:

Central Nervous System

Delirium, EEG abnormal, exacerbation of psychosis, myoclonus, overdose, paresthesia, possible mild cataplexy, ~~and~~ status epilepticus, and obsessive compulsive symptoms

Cardiovascular System

Atrial or ventricular fibrillation and periorbital edema

Gastrointestinal System

Acute pancreatitis, dysphagia, fecal impaction, intestinal obstruction/paralytic ileus, and salivary gland swelling

Hepatobiliary System

Cholestasis, hepatitis, jaundice

Hepatic System

Cholestasis

Urogenital System

Acute interstitial nephritis and priapism

Integumentary (skin)

Hypersensitivity reactions: photosensitivity, vasculitis, erythema multiforme, and Stevens-Johnson Syndrome

Metabolic and Nutritional Disorders

Hypercholesterolemia, ~~very rare and~~ hypertriglyceridemia, ~~very rare~~ and new onset diabetes

Musculoskeletal System

Myasthenic syndrome and rhabdomyolysis

Respiratory System

Aspiration, ~~and~~ pleural effusion, and pneumonia and lower respiratory tract infection which may be fatal

Hemic and Lymphatic System

Deep-vein thrombosis, elevated hemoglobin/hematocrit, ESR increased, pulmonary embolism, sepsis, thrombocytosis, and thrombocytopenia

Vision Disorders

Narrow-angle glaucoma

Miscellaneous

Creatine phosphokinase elevation, hyperglycemia, hyperuricemia, hyponatremia, and weight loss

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, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21590	SUPPL-17	AZUR PHARMA INTERNATIONAL III LTD	FAZACLO (CLOZAPINE) ORALLY DISINTEGRATI

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

/s/

MITCHELL V Mathis
09/08/2010
For Dr. Laughren