



NDA 19-758/S-058

Novartis Pharmaceuticals Corporation  
Attention: Sonia Juan, M.S.  
Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. Juan:

We acknowledge receipt of your supplemental new drug application dated March 14, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clozaril (clozapine HCl) Tablets.

Reference is also made to an e-mail communications dated January 16, 2008 and June 24, 2008 from Dr. Sonny Saini, of this Agency, requesting labeling changes pertaining to acute dystonia, and informing you that these changes were class labeling changes for all antipsychotics.

Your above supplemental application, submitted as a "Prior Approval" supplement, proposed alternative language for Clozaril in regards to this class labeling. However, in your email dated June 26, 2008 you agreed to the Agency's counterproposal language.

We note your agreement to the language below.

Under **ADVERSE REACTIONS**, the addition of a new subsection entitled **Extrapyramidal Symptoms-Dystonia**

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups. Clozapine, an atypical antipsychotic, is associated with a low incidence of dystonia [See Warnings, Tardive Dyskinesia].

Under **Warnings-Tardive Dyskinesia**, the revision of the sentence below.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical

finding that it has a relatively weak dopamine-blocking effect and the clinical finding of a low incidence of certain acute extrapyramidal symptoms, e.g., dystonia.

We have completed our review of this application, and it is approved, effective on the date of this letter with the above agreed upon language.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the above proposed changes to product labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "SPL for approved supplement NDA 19-758/S-058."

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, call LCDR Sonny Saini, Pharm. D., Senior 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

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/s/

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Thomas Laughren  
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