



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-758/S-053

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

Dear Ms. Juan:

Please refer to your supplemental new drug application dated February 24, 2005, received March 3, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clozaril (clozapine HCl) 25 mg and 100 mg Tablets.

Reference is also made to your amendments dated September 24, 2007, and September 18, 2008.

We additionally refer to Agency communications dated March 6, 2006, July 25, 2006, and August 20, 2008.

Your submission of September 24, 2007 constituted a complete response to our March 6, 2006 action letter.

This "Changes Being Effected in 30 days" supplemental new drug application provides for the following labeling changes:

1. The addition of the drug "citalopram" to the list of drugs known to inhibit the activity of cytochrome P450 isozymes and which may increase the plasma levels of clozapine under the **Drug Interactions-Pharmacokinetic Related Interactions** section.
2. The following subsection has been added to the **Other Events Observed During the Premarketing Evaluation of CLOZARIL (clozapine)** section of labeling:

[We note your agreement submitted in your September 24, 2007 amendment to remove the caveat "very rarely" from these terms as requested in our July 25, 2006 action letter.]

Metabolic and Nutritional Disorders: hypercholesterolemia and hypertriglyceridemia

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as agreed upon with the above labeling changes.

Within 21 days of the date of this letter, you **must** 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 includes all of the approved labeling revisions to date. The labeling **must** incorporate the labeling changes approved in Agency letters dated June 26, 2008, and August 14, 2008, for supplemental applications S-058 and S-059, respectively. 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-053".

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 Keith Kiedrow, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1924.

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
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/s/

Thomas Laughren
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