



NDA 19-758 / SLR-051

Novartis Pharmaceuticals Corporation
Attention: James T. Rawls, Pharm.D.
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Rawls:

Please refer to your supplemental new drug application dated November 24, 2003, received November 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clozaril (clozapine) Tablets.

This "Changes Being Effected" supplemental new drug application provides for inclusion of information in labeling, under WARNINGS, regarding diabetes mellitus and hyperglycemia as follows:

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including CLOZARIL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the submitted labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted November 24, 2003).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-758 / SLR-051." Approval of this submission by FDA is not required before the labeling is used.

We believe the safe use of Clozaril can be enhanced by informing prescribers and patients of the addition of "Hyperglycemia and Diabetes Mellitus" labeling information under WARNINGS and request that you issue a letter communicating this important information (i.e., a "Dear Health Care Professional" letter). Please submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug 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/

Russell Katz
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