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NOVARTIS

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IMPORTANT DRUG WARNING

Dear Health Care Provider:

Novartis would like to inform you of recent changes to the WARNINGS section of the prescribing information (PI) for Clozaril® (clozapine) tablets. After reviewing recent data related to the use of atypical antipsycohotics and hyperglycemia with its related symptoms (e.g., polydipsia, polyuria, polyphagia and weakness), the Food and Drug Administration (FDA) concluded that labeling for all atypical antipsychotics should be updated to include information about the potential for these adverse events.

The FDA acknowledges that the relationship between atypical antipsychotic use and hyperglycemia is not completely understood and is confounded by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes in the general population. Although, similar information was previously provided in the PRECAUTIONS section of the PI for Clozaril, Novartis concurs with the FDA that the safe use of atypical antipsychotics can be enhanced by informing patients and prescribers about these adverse events within the WARNINGS section of the PI. The text of this new WARNINGS statement follows below. All patients being treated with Clozaril and their caregivers should be fully informed of this increased risk of hyperglycemia and diabetes. Additionally, the enclosed revised product labeling reflects this new information, which is also conveniently available at http://www.clozaril.com/index.jsp.

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.

Novartis is committed to providing you with the most current product information available for the management of patients receiving Clozaril. You can further our understanding of adverse events by reporting them.

Healthcare professionals should report all serious adverse events suspected to be associated with use of Clozaril to Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936 by phone (888) NOW-NOVARTIS or (888-669-6682) or the internet at http://www.novartis.com/contact/en/index.shtml.

Alternatively, this information may be reported to the FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by fax 1-800-FDA-0178, by mail using the Form 3500 at MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20857 or the internet at http://www.accessdata.FDA.gov/scripts/medwatch.

Sincerely,

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Clinical Safety and Epidemiology

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