NOVARTIS

September 22, 2000

IMPORTANT
DRUG
WARNING

Dear Doctor or Pharmacist:

This communication is to advise you of important prescribing information changes for Serentil® (mesoridazine besylate) tablets, 25 and 50 mg. Serentil has been shown to prolong the QTc interval in a dose related manner, and drugs with this potential, including Serentil, have been associated with torsade de pointes-type arrhythmias and sudden death. Therefore, the following major modifications to the use of Serentil must be immediately implemented:

- Serentil is now indicated **only** for schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects. Notwithstanding, Serentil has not been systematically evaluated in controlled trials in treatment refractory schizophrenic patients and its efficacy in such patients is unknown.

- Serentil is now contraindicated with other drugs known to prolong the QTc interval as well as in patients with congenital long QT syndrome or a history of cardiac arrhythmias.

- Patients being considered for treatment with Serentil should have a baseline ECG performed and serum potassium levels measured. Serum potassium should be normalized before starting treatment and patients with a QTc interval greater than 450 msec should not receive Serentil. Periodic ECG's and serum potassium levels during Serentil treatment may be useful and Serentil should be discontinued in patients who are found to have a QTc interval over 500 msec.

- Treatment of Serentil overdosage should entail immediate cardiovascular monitoring, to include continuous electrocardiographic monitoring to detect arrhythmias. Drugs that may produce

additive QT-prolonging effects, such as disopyramide, procainamide, and quinidine, should be avoided in the treatment of Serentil overdosage.

These changes to the use of the product are based primarily on the findings reported in a published study involving nine schizophrenic patients who had normal ECG tracings at baseline, a washout of prior psychotropic medication, and no significant cardiovascular, renal, or liver disease[1]. These patients were treated with mesoridazine 75 mg/day for week 1, 200 mg/day for week 2, and 300 mg/day for weeks 3 and 4. ECG tracings were obtained at baseline, during weeks 2, 3, and 4, and two weeks after drug discontinuation. At the lowest dose (75mg), 4 of 9 patients displayed mild to moderate prolongation of the QT interval. At the highest dose (300mg), all 9 patients had moderate prolongation of the QT interval. Two weeks after discontinuation, ECG's for 8 of the 9 patients had normalized. There were no reports of syncope or other serious adverse experiences in this study. Five of the patients did experience mild orthostatic hypotension.

Prolongation of the QTc interval has been associated with torsade de pointes-type arrhythmias and sudden death. There have been three published case reports of ventricular tachycardia, one with lethal outcome, in association with mesoridazine overdosage[2,3,4]. A causal relationship between these events and mesoridazine therapy has not been established but, given the ability of mesoridazine to prolong the QTc interval, such a relationship is possible.

It is reasonable to assume that the co-administration of medications that prolong the QTc interval with Serentil would produce additive prolongation of the QTc interval. Therefore, the co-administration of Serentil with such drugs (e.g., quinidine) is now contraindicated.

Furthermore, patients with congenital long QT syndrome or a history of cardiac arrhythmias may be at increased risk for cardiac arrhythmias in the context of mesoridazine-associated QTc interval prolongation. Thus, Serentil is contraindicated in such patients as well.

Patients currently being treated with Serentil should be fully informed of the above information. Switching to a different antipsychotic agent should be considered and a decision regarding continuation of Serentil treatment should be based on a careful assessment of the potential benefits and risks of Serentil for each patient. Please note that thioridazine, a metabolic precursor of mesoridazine, also appears to have the capacity to prolong the QTc interval.

Sincerely,

Beat Sümegi, MD Vice-President, Medical

Guy Rousseau, PhD
Vice-President, Drug Regulatory Affairs

References

1 Dillenkoffer RL, et al. Electrocardiographic Evaluation of Mesoridazine (Serentil). Current Therapeutic Research 1972;14(2):71-72.

2 Marrs-Simon PA, et al. Cardiotoxic manifestations of mesoridazine overdose. Ann Emerg Med 1988; 17(10):1984-90.

3 Niemann JT, et al. Cardiac conduction and rhythm disturbances following suicidal ingestion of mesoridazine. Ann Emerg Med 1981; 10(l 1): 585-8

4 Vertrees JE and Siebel G. Rapid death resulting from mesoridazine overdose. Vet Hum Toxicol 1987;29(l):65-7.

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

Novartis Pharmaceuticals Canada Inc., 385 Bouchard Boulevard, Dorval, Quebec, H9S 1A9 by phone at (800) 363-8883 or by fax at (514) 636-3175

or

Adverse Reaction Review and Information Unit,
Adverse Reaction and Medication Error Assessment Division,
Bureau of Licensed Product Assessment,
Therapeutic Products Programme,
Health Canada, Finance Building
Address Locator 0201C2,
Ottawa, Ontario K1A 1B9;

ADR Report Forms can be found in *The Canadian Compendium of Pharmaceutical and Specialties* or the TPP website at:

http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf

or by contacting the Adverse Reaction Review and Information Unit at tel.: (613) 957-0337 or fax (613) 957-0335.