NOVARTIS

July 31, 2000

**IMPORTANT**
**DRUG**
**WARNING**

Dear Doctor or Pharmacist:

This communication is to advise you of important prescribing information applicable to Mellaril® (thioridazine HCl). **Mellaril has been shown to prolong the QTc interval in a dose related manner, and drugs with this potential, including Mellaril, have been associated with torsade de pointes-type arrhythmias and sudden death**. Therefore, the following major modifications to the use of Mellaril must be immediately implemented:

Mellaril 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, Mellaril has not been systematically evaluated in controlled trials in treatment of refractory schizophrenic patients and its efficacy in such patients is unknown.

Mellaril is now contraindicated with certain other drugs, including fluvoxamine, propranolol, pindolol, any drug that inhibits the cytochrome P450 2D6 isozyme, e.g., fluoxetine and paroxetine, and agents known to prolong the QTc interval; Mellaril is also contraindicated in patients known to have reduced levels of the cytochrome P450 2D6 isozyme as well as in patients with congenital long QT syndrome or a history of cardiac arrhythmias;

Patients being considered for treatment with Mellaril 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 Mellaril. Periodic ECG's and serum potassium levels during Mellaril treatment may be useful and Mellaril should be discontinued in patients who are found to have a QTc interval over 500 msec.

Treatment of Mellaril 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 Mellaril overdosage.

These changes to the use of the product are based primarily on the findings reported in three published studies.

The first of these investigations, a randomized, double-blind, three-period crossover study in nine healthy males following single dose exposure to placebo or one of two thioridazine doses (10 mg or 50 mg), with a one week or longer washout between treatment periods, showed cardiac effects related to the plasma concentration of thioridazine and its metabolites. Among these, this study reported a dose-related prolongation of the QTc interval between 2 and 8 hours after thioridazine administration. Following dosing with thioridazine 50 mg, the mean QTc increased from 388 (SD±18) to 411 (SD±14) msec four hours post-dose, with a mean maximal increase of 23 msec. This change was statistically significantly greater than that for either placebo or thioridazine 10 mg (<0.01 and <0.05, respectively).[1]

The second recent study demonstrated altered pharmacokinetics and increased serum levels of thioridazine in patients with a genetic defect resulting in slow hydroxylation of debrisoquin. This genetic defect is present in about 7% of the Caucasian population. This study examined results from a single 25 mg oral dose of thioridazine in 19 healthy subjects: 6 slow and 13 rapid hydroxylators of debrisoquin. The slow hydroxylators obtained higher serum levels of thioridazine with a 2.4-fold higher Cmax and a 4.5-fold larger AUC associated with a twofold longer half-life compared with that of the rapid hydroxylators.[2]

The rate of debrisoquin hydroxylation appears to depend on the activity level of the cytochrome P450 2D6 isozyme. Thus, this study suggests that the co-administration of Mellaril with drugs that inhibit this isozyme and the use of Mellaril in patients with reduced levels of activity of this isozyme will result in substantial elevation of thioridazine plasma levels.

The third recent study evaluated the effect of fluvoxamine (25 mg bid for one week) on thioridazine steady state concentration in 10 male inpatients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased three-fold following co-administration of fluvoxamine.[3]

Prolongation of the QTc interval has been associated with torsade de pointes-type arrhythmias and sudden death. There are several published case reports of torsade de pointes and sudden death associated with thioridazine treatment. A causal relationship between these events and thioridazine therapy has not been established but, given the ability of thioridazine to prolong the QTc interval, such a relationship is possible.

Since the degree of QTc interval prolongation appears to be related to the dose of thioridazine, it is reasonable to assume that concomitant medications or other factors, which produce elevations in thioridazine plasma levels, will increase the degree of QTc prolongation and possibly increase the risk of serious ventricular arrhythmias. In addition, the co-administration of Mellaril with other drugs that prolong the QTc interval is expected to produce additive prolongation of the QTc interval. Therefore, the co-administration of Mellaril with inhibitors of cytochrome P450 2D6, e.g., fluoxetine and paroxetine, drugs that prolong the QTc interval, fluvoxamine, propranolol, or pindolol is now contraindicated. For the same reason, Mellaril is also contraindicated in patients known to have reduced levels of cytochrome P450 2D6.

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 thioridazine- associated QTc interval prolongation. Thus, Mellaril is contraindicated in such patients as well.

Patients currently being treated with Mellaril should be fully informed of the above information. Switching to a different antipsychotic agent should be considered and a decision regarding continuation of Mellaril treatment should be based on a careful assessment of the potential benefits and risks of Mellaril for each patient. Please note that mesoridazine, the active ingredient of Serentil®, is the major active metabolite of Mellaril and 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 Hartigan-Go K, et al. Concentration-related pharmacodynamic effects of thioridazine and its metabolites in humans. Clin Pharmacol Ther 1996;60:543-553.

2 vonBahr C, et al. Plasma levels of thioridazine and metabolites are influenced by the debrisoquin hydroxylation phenotype. Clin Pharmacol Ther 1991:49(3):234-240.

3 Carillo JA, et al. Pharmacokinetic Interaction of Fluvoxamine and Thioridazine in Schizophrenic Patients. J Clin Psychopharmacol 1999;19:494-499.


Novartis is committed to providing you with the most current product information available for the management of patients receiving Mellaril. 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.

You can also report adverse drug reactions to the:

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, Tunney's Pasture,
Address Locator 0201C2,
Ottawa, Ontario K1A 1B9

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