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Contact the company for a copy of any references, attachments or enclosures.

IMPORTANT
DRUG SAFETY
INFORMATION

NOVARTIS

January 14, 2002

Subject : Association of CLOZARIL (clozapine) with cardiovascular toxicity

Dear Healthcare Professional:

Novartis Pharmaceuticals Canada Inc., following discussions with Health Canada, is alerting you to important emerging safety information regarding a constellation of cardiovascular events that have been reported in patients treated with Clozaril* (clozapine). The following information will be incorporated into the Product Monograph.

CARDIOVASCULAR TOXICITY:

Analysis of safety databases suggests that the use of clozapine is associated with an increased risk of myocarditis especially during, but not limited to, the first month of therapy. Myocarditis has been reported in patients 19 years of age and older, at dosages within the approved dosage range and during titration of clozapine. In Canada, there have been 9 reported cases of myocarditis. Of these, three have been fatal. Given the estimated 15,600 Canadian clozapine-treated patients as of August 2001, this represents an estimated incidence of 0.06% for all reports of myocarditis (or 1/1667 patients) and 0.02% for myocarditis fatalities (or 1/5200).

Pericarditis, pericardial effusion and cardiomyopathy have also been reported in association with clozapine use, as have heart failure, myocardial infarction and mitral insufficiency; these reports include fatalities.

In patients who develop persistent tachycardia at rest accompanied by other signs and symptoms of heart failure (e.g. chest pain, tachypnoea (shortness of breath), or arrhythmias), the possibility of myocarditis, cardiomyopathy and/or other cardiovascular dysfunction must be considered. Other symptoms which may be present in addition to the above include fatigue, flu-like symptoms, fever that is otherwise unexplained, hypotension and/or raised jugular venous pressure.

The occurrence of such signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, cardiomyopathy and/or other cardiovascular dysfunction by a cardiologist. Patients with a family history of heart failure should have a cardiac evaluation prior to commencing treatment; clozapine is contraindicated in patients with severe cardiac disease.

In patients in whom myocarditis is suspected, clozapine treatment should be promptly discontinued. Patients with clozapine-induced myocarditis should not be re-exposed to clozapine.

If cardiomyopathy and/or other cardiovascular dysfunction is diagnosed, discontinuation of clozapine, based on clinical grounds, should be considered.

Further information will be provided on these issues as it becomes available.

BACKGROUND INFORMATION:

A Myocarditis, pericarditis and pericardial effusion

Myocarditis and pericarditis/pericardial effusion, including fatalities, have been reported in patients 19 years of age and older, at dosages within the approved dosage range and during titration of clozapine, and emerging within the first few weeks of clozapine administration. Recurrences of myocarditis upon rechallenge with clozapine have been documented. Eosinophilia has been co-reported in some cases and thus such cardiovascular adverse events associated with clozapine use may represent hypersensitivity reactions to clozapine; it is not known, however, whether eosinophilia is a reliable predictor of carditis.

In Canada, a total of 16 post-marketing surveillance spontaneous reports of myocarditis/pericarditis/pericardial effusion have been received by Health Canada. Of these, a total of 9 Canadian reports of myocarditis, three of which are known to have been fatal, have been received by Health Canada. The age range for cases of myocarditis reported in Canada was 19-37 years. The shortest known clozapine treatment duration was 2 weeks. Many of these patients were prescribed clozapine within approved dosage recommendations or were being titrated. Given the estimated 15,600 Canadian clozapine-treated patients as of August 2001, this represents an incidence of 0.06% for all reports of myocarditis (or 1/1667 patients) and 0.02% for myocarditis fatalities.

The reporting incidences for myocarditis from the four countries (USA, United Kingdom, and Canada, data through August 2001, and Australia, data through March 1999) with Clozaril national registries can reliably be calculated. These incidences are, however, divergent, with the lowest rate reported in the U.S. (1/20 000 person years) and the highest rate reported in Australia (1/800 person years). In these 4 countries, a total of 81 reports of myocarditis have been identified by Novartis from spontaneous reporting/post-marketing surveillance data in approximately 253,000 patients. Thirty of these cases were fatal, with 24 of the 30 cases (80%) showing evidence of myocarditis at autopsy. Overall, the Novartis international pharmacovigilance database contains 213 reports of myocarditis out of an estimated 3,000,000 patient-years of exposure to clozapine (1/14000 patient years). Fifty of these had a fatal outcome and 85% of cases of myocarditis occurred within the first two months of initiation of therapy with clozapine. International post-marketing reports of pericarditis/pericardial effusion, with or without eosinophilia, have also been identified; some of these have been fatal.

Another analysis of international data on clozapine and myocarditis revealed that almost 40% of patients were under the age of 30 years and 34% were between 30 and 49 years of age. Thus, the occurrence of myocarditis appears to be independent of age and therefore can occur in younger patients. Most patients were prescribed clozapine between 200 and 500 mg per day and thus dosages were mostly in accordance with current labelled dosage recommendations, the recommended daily dose being 300 - 450 mg . Twenty two patients (33 %) were taking less than 300 mg/day of clozapine and of these, 10 were on less than 200 mg/day; this may reflect the fact that the event occurred in the early treatment stage during dose titration.

B Cardiomyopathy/heart failure/mitral insufficiency

In Canada, seven cases of cardiomyopathy and 3 cases of heart failure/mitral insufficiency have been reported to Health Canada, with individual cases reported to have concomitant myocarditis or endocarditis (age range for cardiomyopathy reports: 19-55 years; 6 patients under age 50 years); two of the reports of heart failure are known to have been fatal (61y male, 46y male).

A total of 178 cardiomyopathy reports (32 fatal), from early 1969 to mid-August 2001 have been received by Novartis from all international spontaneous reporting/post-marketing surveillance i.e. from countries in addition to Canada, US, UK and Australia.

Demographics of the analysis of the 178 cases revealed that four times as many men as women were diagnosed with cardiomyopathy. In patients 15-44 years of age, the incidence rate of spontaneous reports of cardiomyopathy in clozapine-treated patients was greater than in the general population in either the U.S. or in established international market economies. Cardiomyopathy was confirmed at autopsy in 14 (7.9%) of reports and by echocardiography in 63 (36%) of cases. About 80% of the cases occurred in patients under the age of 50. The typical clozapine dose range was between 201 mg/d and 500 mg/d and the duration of treatment was more than 6 months in 65% of the patients. Only ten percent of patients were reported to be co-medicated with other antipsychotics while taking clozapine. There was no other apparent cause of the cardiomyopathy in about 50% of all reported cases of cardiomyopathy and in 28% of fatalities (e.g. other drugs known to be associated with cardiomyopathy, alcohol or drug abuse, history of arteriosclerotic cardiovascular disease (ASCVD), hypertension (HTN), diabetes mellitus or obesity); the average age of these patients without other known association for cardiomyopathy was approximately 37 years. The following associated terms were co-reported with cardiomyopathy: congestive heart failure (21%), cardiomegaly (8%), heart rate and rhythm disorders (10%), left ventricular dilatation (4%), sudden unexplained death (2 patients) and cardiac arrest (1 report). Dilated cardiomyopathy represented two-thirds of all cases and 41% of deaths and cardiomyopathy Not Otherwise Specified (NOS) about 40% of cases and 25% of the deaths. Of the reports of dilated cardiomyopathy, 9 included the term myocarditis, 3 included the term pleural effusion and 2 included the term fibrosis.

In the 4 cases where follow-up was reported after withdrawal of clozapine, there was improvement of the cardiomyopathy.

C Myocardial infarction

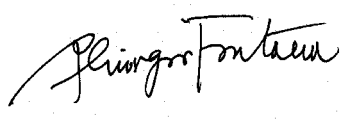
In Canada, 30 reports of myocardial infarction in patients receiving clozapine have been received by Health Canada since marketing in 1991; the earliest of these was reported in 1995; 15 of these are known to have been fatal (age range: 37y - 82y). Causality has not been established at this time.

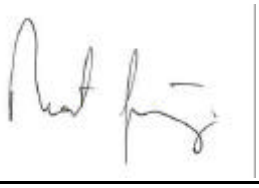
NOTE: Due to varied regulations in some jurisdictions, numbers of officially reported adverse events represent only a small fraction of actual events. As only a small proportion of suspected adverse events are usually reported, caution should be exercised in estimating the incidence of adverse events.

The revised Product Monograph will be available to Healthcare Professionals upon request. A Public Advisory will be released within one week of the issuance of this Dear Healthcare Professional Letter. Current and future clozapine-treated patients should be fully informed of the above information.

Further information on these issues will be provided as it becomes available.

Sincerely,





Pier-Giorgio Fontana, PhD
Vice-President, Drug Regulatory Affairs

Beat Sümegi, MD
Vice-President, Medical

* Clozaril is a registered Trademark of Novartis Pharmaceuticals Canada Inc.

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

Any suspected adverse drug reactions can also be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Bureau of Licensed Product Assessment
Therapeutic Products Directorate
HEALTH CANADA
Address Locator: 0201C2
OTTAWA, Ontario, K1A 1B9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll free for consumers and health professionals:
Tel: 866 234-2345, Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

The ADR Reporting Form can be found in *The Canadian Compendium of Pharmaceuticals and Specialties*, or on the TPD web site, along with the ADR Guidelines at:

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