Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

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IMPORTANT
DRUG
WARNING

Dear Health Care Provider:

Novartis would like to inform you of recent changes to the BOXED WARNING and WARNINGS sections of the prescribing information (PI) for Clozaril® (clozapine) as follows:

- The previously existing BOXED WARNING has been relocated to the beginning of the PI and revised to advise health care providers of the association of myocarditis with clozapine therapy.
- A subsection has been added to the WARNINGS section entitled "Myocarditis" to provide data and clozapine treatment guidelines related to this issue.

Post-marketing surveillance data from four countries that employ hematological monitoring of clozapine-treated patients revealed: 30 reports of myocarditis with 17 fatalities in 205,493 U.S. patients (August 2001); 7 reports of myocarditis with 1 fatality in 15,600 Canadian patients (August 2001); 30 reports of myocarditis with 8 fatalities in 24,108 U.K. patients (August 2001); 15 reports of myocarditis with 5 fatalities in 8,000 Australian patients (March 1999). These reports represent an incidence of 5.0, 16.3, 43.2, and 96.6 cases/100,000 patient years, respectively. The number of fatalities represent an incidence of 2.8, 2.3, 11.5, and 32.2 cases/100,000 patient years, respectively.

The possibility of myocarditis should be considered in patients receiving clozapine who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST- T wave abnormalities or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. Tachycardia, which has been associated with clozapine treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis.

The prompt discontinuation of clozapine therapy is warranted upon suspicion of myocarditis. Patients with clozapine-induced myocarditis should not be rechallenged with clozapine.

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.

Health care professionals should report all serious adverse events suspected to be associated with use of Clozaril® (clozapine) to Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936, or by phone at (800) 448-5938 or the internet at http://www.novartis.com.

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.

Please see the enclosed revised PI for complete prescribing information. Future and current patients being treated with Clozaril® (clozapine) should be fully informed of the above information.

Alan L. Bess, M.D.
Vice President
Clinical Safety & Epidemiology

Stephen R. Cunningham, M.D., FRCP, FFPM
Vice President
Medical Affairs