NATIONAL PBM RESPONSE
to FDA Information for Healthcare Professionals Regarding Mitoxantrone
August 18, 2008

The Food and Drug Administration (FDA) and the manufacturers of mitoxantrone recommend additional monitoring to detect late-onset cardiac toxicity via annual left ventricular ejection fraction (LVEF) evaluations in all patients with multiple sclerosis (MS) who received and completed treatment with mitoxantrone. This recommendation is based on a post-marketing study using insurance claims data and chart review that suggested non-compliance with cardiac monitoring, specifically quantitative LVEF monitoring, in a majority of patients with MS treated with mitoxantrone. In this study, four patients developed congestive heart failure (CHF) up to 17 months after finishing therapy with mitoxantrone. [1]

Previous product labeling changes for mitoxantrone in March 2005 include recommendations for LVEF evaluation prior to starting therapy with mitoxantrone as well as before the administration of each dose in patients with MS. These labeling changes were based on post-marketing reports and case reports in the medical literature of decreased LVEF and development of CHF in patients with MS receiving total doses of mitoxantrone below 100 mg/m^2. CHF can develop within months to years after completion of mitoxantrone therapy. [1] **It is important to detect asymptomatic decreases to LVEF to ensure that appropriate therapy is initiated. Waiting to perform monitoring until a patient becomes symptomatic could delay initiation of therapy. The current FDA recommendation is to perform LVEF testing prior to initiation of mitoxantrone therapy, before each dose of mitoxantrone and on a yearly basis after therapy is completed.**

An analysis conducted by Ghalie et al, found that out of 1,378 patients, 779 completed baseline and scheduled follow-up LVEF testing. The observed incidence of CHF in patients with MS who received a mean cumulative dose of 60.5 mg/m2 of mitoxantrone was 0.20%. [2] **A phase IV study of long-term safety and tolerability is currently under way in 509 MS patients aged 18 to 65 years who have been treated with mitoxantrone. A total of 509 patients have been enrolled in the study. Asymptomatic depression of LVEF by ≥10% from baseline has occurred in 23 individuals, and 29 others have increased LVEF ≥10%.** [3]

A query of the VA Adverse Drug Event Reporting System (VA ADERS) from March 2007 to July 30, 2008, revealed no reports of cardiovascular adverse drug events associated with mitoxantrone use.

Please refer to the FDA Information for Healthcare Professionals for detailed information available at the following link: http://www.fda.gov/cder/drug/InfoSheets/HCP/mitroxantroneHCP.htm.

REFERENCES

1. Food and Drug Administration (FDA) Alert. 07/29/2008. http://www.fda.gov/cder/drug/InfoSheets/HCP/mitroxantroneHCP.htm.
2. Ghalie RG, Edan G, Laurent M, et al. Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. Neurology 2002;59:909–913.
3. Smith CH, Lopez-Bresnahan MV, Beagan J. Safety and tolerability of Novantrone_ (mitoxantrone) in clinical practice: status report from the Registry to Evaluate Novantrone Effects in Worsening MS (RENEW)Study. Neurology 2004;62(suppl 5):A489. Abstract.