

April 2005

Dear Healthcare Professional:

This letter is sent to you to supplement previously provided information concerning the risks of cardiotoxicity associated with NOVANTRONE[®] (mitoxantrone for injection concentrate) treatment for multiple sclerosis (MS) and also provides supplemental information regarding secondary acute myelogenous leukemia (AML) reported in MS patients treated with NOVANTRONE[®].

Reports received through post-marketing surveillance, have shown that diminished cardiac function may occur early on in the treatment with NOVANTRONE[®]. Therefore, the Product Labeling for NOVANTRONE[®] was updated in March 2005 to state that cardiac monitoring of MS patients should be performed at baseline and prior to administration of **every** dose of NOVANTRONE[®]. Please refer to the Product Labeling (enclosed) for full prescribing information, including the specific sections on "Boxed Warnings," "Warnings," and "Dosage and Administration."

NOVANTRONE[®] is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses). NOVANTRONE[®] is not indicated in the treatment of patients with primary progressive multiple sclerosis.

Cardiotoxicity

As stated in the Boxed Warning within the Prescribing Information for NOVANTRONE[®],

Use of NOVANTRONE[®] has been associated with cardiotoxicity. Cardiotoxicity can occur at any time during NOVANTRONE[®] therapy, and the risk increases with cumulative dose. Congestive heart failure (CHF), potentially fatal, may occur either during therapy with NOVANTRONE[®] or months to years after termination of therapy. All patients should be carefully assessed for cardiac signs and symptoms by history and physical examination prior to start of NOVANTRONE[®] therapy. Baseline evaluation of left ventricular ejection fraction (LVEF) by echocardiogram or multi-gated radionuclide angiography (MUGA) should be performed. Multiple sclerosis patients with a baseline LVEF <50% should not be treated with NOVANTRONE[®]. LVEF should be reevaluated by echocardiogram or MUGA prior to each dose administered to patients with multiple sclerosis. Additional doses of NOVANTRONE[®] should not be administered to multiple sclerosis patients who have experienced either a drop in LVEF to below 50% or a clinically significant reduction in LVEF during NOVANTRONE[®] therapy. Patients with multiple sclerosis should not receive a cumulative dose greater than 140 mg/m². In cancer patients, the risk of symptomatic congestive heart failure (CHF)

was estimated to be 2.6% for patients receiving up to a cumulative dose of 140 mg/m². Presence or history of cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with NOVANTRONE[®] may occur whether or not cardiac risk factors are present. For additional information see **WARNINGS, Cardiac Effects**, and **DOSAGE AND ADMINISTRATION**.

As stated in the WARNINGS section,

LVEF should be evaluated by echocardiogram or MUGA prior to administration of the initial dose of NOVANTRONE[®]. Multiple sclerosis patients with a baseline LVEF of <50% should not be treated with NOVANTRONE[®]. Subsequent LVEF evaluations are recommended if signs or symptoms of congestive heart failure develop, and prior to all doses administered to multiple sclerosis patients. NOVANTRONE[®] should not be administered to multiple sclerosis patients with an LVEF of <50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of ≥140 mg/m².

Secondary Leukemia (AML)

As stated in the Boxed Warning within the Prescribing Information for NOVANTRONE[®],

Secondary acute myelogenous leukemia (AML) has been reported in multiple sclerosis and cancer patients treated with mitoxantrone. In a cohort of mitoxantrone treated MS patients followed for varying periods of time, an elevated leukemia risk of 0.25% (2/802) has been observed. Postmarketing cases of secondary AML have also been reported. In 1774 patients with breast cancer who received NOVANTRONE[®] concomitantly with other cytotoxic agents and radiotherapy, the cumulative risk of developing treatment-related AML, was estimated as 1.1% and 1.6% at 5 and 10 years, respectively (see **WARNINGS** section). Secondary acute myelogeneous leukemia (AML) has been reported in cancer patients treated with anthracyclines. NOVANTRONE[®] is an anthracenedione, a related drug.

The occurrence of refractory secondary leukemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated.

Cases of secondary AML in MS patients treated with NOVANTRONE[®] have been reported in peer-reviewed literature, through the collection of spontaneous reports, and in a prospective observational study (see below). Because the number of MS patients exposed to NOVANTRONE[®] in post-marketing is unknown and because spontaneous reporting of adverse events can be subject to under-reporting, it is not possible to determine incidence—or relative risk to an MS patient—of developing secondary AML.

