Novantrone®
mitoxantrone
for injection concentrate

serono

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/m^2. 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/m^2. 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/m^2.

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.
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> 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.

The Registry to Evaluate NOVANTRONE® Effects in Worsening MS (RENEW) is an ongoing 5-year, post-marketing, observational study involving a cohort of 505 patients with worsening relapsing-remitting, secondary progressive, or progressive-relapsing MS. Since initiation of patient enrollment in April 2001, there has been one case of secondary AML reported, involving a 52-year-old female with secondary progressive multiple sclerosis. She had received a cumulative total of 72 mg/m^2 of NOVANTRONE®, in six infusions given from August 2001 to December 2002, when she was noted to be neutropenic, at which time her treatment with NOVANTRONE® was stopped. In May 2004, she was noted to have peripheral blasts and bone marrow biopsy confirmed AML. This patient had no other known risk factors for leukemia and no concomitant potentially cytotoxic drugs were listed. Her AML was considered probably related to NOVANTRONE®. Since treatment with idarubicin and ara-C, she has been in remission. Based on this case, the incidence rate in this study is increased as compared to a non-exposed matched population.

Because of the risk of secondary AML, strict adherence to existing blood cell count monitoring recommendations for patients being treated with NOVANTRONE® for MS should be followed with complete blood counts, including platelets, prior to each course of NOVANTRONE® and in the event that signs or symptoms of infection develop. NOVANTRONE® generally should not be administered to MS patients with neutrophil counts less than 1500 cells/mm^3. Also, regular blood cell counts should be monitored after discontinuation of NOVANTRONE® therapy.

Prescribers are advised to adhere to the monitoring recommendations made in the Prescribing Information and to make a careful risk-benefit assessment of the use of NOVANTRONE® in their MS and oncology patients.

If you have any questions regarding this important safety information, please contact Serono Medical Information at 1-888-ASK-SERO (1-888-275-7376). Serono is committed to ensuring that NOVANTRONE® is used safely and effectively and to providing you with the most current labeling information for NOVANTRONE®.

Healthcare professionals should report any serious adverse event suspected to be associated with the use of NOVANTRONE® or any of Serono's products to US Product Surveillance at 1-800-283-8088 extension 5563 or fax to 1-781-681-2961. Alternatively, this information may be reported to the FDA's MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), by e-mail (www.fda.gov/medwatch), or by postal mail (with the MedWatch form FDA 3500A) to FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Yours sincerely,

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Encl: Prescribing Information for NOVANTRONE®, March 2005