

PATIENT INFORMATION

NOVANTRONE (noe-VAN-trone)

mitoxantrone
for injection concentrate

SERONO

For Treating Multiple Sclerosis

Read this information carefully before you start taking NOVOVANTRONE for multiple sclerosis (MS). This information does not take the place of talking with your doctor. Your doctor can tell you more about NOVANTRONE and answer any questions you have about this treatment.

NOVANTRONE is used for other conditions besides MS. This leaflet has information about using NOVANTRONE specifically for MS.

What is the most important information I should know about NOVANTRONE?

NOVANTRONE can reduce relapses and disability for patients with worsening forms of MS.

- NOVANTRONE may damage your heart at any time during therapy or months to years after therapy ends. Heart damage caused by NOVANTRONE can be serious and may cause death. Your doctor will perform certain tests to see that your heart is working normally before you start to take NOVANTRONE. Your doctor will repeat these heart tests before you receive each additional dose. Your doctor will also perform these tests if you have any symptoms of heart problems. Because the risk to your heart may depend on the total amount of NOVANTRONE given, your doctor will limit the number of doses you get. Most patients will reach this limit after about 8 to 12 doses given over 2 to 3 years. After you have reached your limit, you should not receive any additional NOVANTRONE. You and your doctor should both keep track of

how much NOVANTRONE you get. (See the sections “**What diagnostic tests will be performed?**” and “**What are the possible side effects of NOVANTRONE?**”)

NOVANTRONE can increase your chance of getting an infection. If you begin to have any signs of infection, such as fever, chills, sore throat, cough, pain with urinating, or urinating more often, call your doctor right away. If you have such an infection, it can usually be treated by taking antibiotics.

MS and cancer patients treated with NOVANTRONE have an increased risk of developing leukemia.

What is NOVANTRONE?

NOVANTRONE is a medicine to treat MS patients with secondary (chronic) progressive, progressing relapsing, or worsening relapsing-remitting MS. It is not for treating primary progressive MS. Patients treated with NOVANTRONE may have fewer relapses and keep their mobility longer.

Who should not take NOVANTRONE?

Women who are pregnant, are trying to become pregnant, or are breastfeeding should not take NOVANTRONE because it may harm the baby. You should use birth control while taking NOVANTRONE to avoid becoming pregnant. Your doctor should also give you a pregnancy test before each dose, and you should know the results of this test before you get each dose of NOVANTRONE. If you plan on getting pregnant, talk with your doctor about stopping the NOVANTRONE treatments. If you do become pregnant, contact your doctor right away.

You should not take NOVANTRONE if your doctor finds you have a low number of white blood cells (leukocytes).

You should not take NOVANTRONE if our doctor finds heart’s ability to pump blood is decreased.

If you are allergic to NOVANTRONE, you should not take it. The active ingredient is mitoxantrone. Ask your doctor about the inactive ingredients.

Your doctor needs to know the following information about you to help decide if NOVANTRONE is right for you. Tell your doctor if you have now or had in the past

- heart diseases
- treatment with NOVANTRONE
- cancer chemotherapy treatment
- radiation treatment to the chest area
- blood-clotting problems
- anemia or low red blood cell counts
- low white blood cell counts
- unusual or unexpected bleeding
- infections
- liver disease or problems
- any known allergies or sensitivities

Also tell your doctor if you take other medicines, including nonprescription medicines and nutritional supplements.

How do I take NOVANTRONE?

NOVANTRONE is given through a needle placed in a vein in your arm. The dose takes about 5 to 15 minutes to deliver. NOVANTRONE treatment is usually given once every 3 months for about 2 to 3 years (8 to 12 doses). However, this may differ for different patients.

What diagnostic tests will be performed?

You will need to have regular testing of your heart and blood to help avoid serious side effects.

Before each dose of NOVANTRONE, your doctor will take blood samples to check your blood counts and liver function. Your doctor may also take a blood sample if you begin to have signs of an infection. If you are a woman who is capable of becoming pregnant, even if you were using birth control, you must have a pregnancy test before each NOVANTRONE dose, and you should know the results before you receive each NOVANTRONE dose.

To measure possible changes to the heart, you should have regular testing of your heart's ability to pump blood. This requires taking pictures of your heart using a simple, painless test such as an

echocardiogram. Your heart should be tested before each dose of NOVANTRONE, or if you show signs of heart problems.

You and your doctor should carefully track the total amount of NOVANTRONE you get. Your doctor may stop NOVANTRONE if your tests show that your heart's ability to pump blood has decreased. If you change doctors, make sure your new doctor knows how much NOVANTRONE you have taken.

What should I avoid while taking NOVANTRONE?

Women should not become pregnant or breastfeed while taking NOVANTRONE because it may harm the baby. Talk with your doctor about effective birth control. Tell your doctor if you become pregnant.

Talk with your doctor about any medicines you currently take and any medicines you plan to start or stop taking. These include prescription and non-prescription medicines and nutritional supplements. Some medicines may affect how NOVANTRONE works.

What are the possible side effects of NOVANTRONE?

Most side effects of NOVANTRONE are not severe and can normally be treated by your doctor. The most common side effects of NOVANTRONE in patients with MS are nausea, hair thinning, loss of menstrual periods, bladder infections, and mouth sores. The nausea is usually mild and generally lasts for less than 24 hours. A small number of patients treated with NOVANTRONE develop heart problems. Tell your doctor if you have trouble breathing, swelling of your legs or ankles, or uneven or fast heartbeat.

NOVANTRONE may cause your white blood cell count to go down, which increases your chance of getting an infection. This risk is greatest within one month after each dose. In addition, NOVANTRONE may cause your platelet count to go down, which increases your chance of bleeding. Call your doctor right away if you begin to have fever, chills, sore throat, cough, pain with urination, urination more often, or if you notice any unusual bleeding or bruising.

NOVANTRONE is dark blue in color, so it may turn your urine a blue-green color for a few days after each dose. The white part of your eyes may also have a slight blue color.

Other side effects may occur be sure to tell your doctor about any side effects whether or not they are listed here.

General advice about prescription medicines

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. If you have any concerns about NOVANTRONE, ask your doctor. Your doctor can give you information about NOVANTRONE that was written for health care professionals. For more information call MS LifeLines toll free at 1-877-447-3243.

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Novantrone

mitoxantrone

For injection concentrate

SERONO

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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 concomitant 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 myelogenous 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.

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/m² 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/mm³. 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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Chief Medical Officer, Serono Inc.