Patient Guide

Mitoxantron® (Mitoxantrone Hydrochloride)

SANDOZ A Novartis Division

Patient Guide

Read this Guide before you start receiving mitoxantrone and each time you receive mitoxantrone for the treatment of multiple sclerosis. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

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

Mitoxantrone can cause serious side effects, including:

- **Heart problems** that may lead to death even in people who have never had heart problems before. Heart failure can happen while you receive mitoxantrone, or months to years after you stop receiving mitoxantrone. Your risk of heart failure increases the more mitoxantrone you receive.

Call your doctor or get medical help right away if you have any of these problems during or after treatment with mitoxantrone:

- shortness of breath
- swelling of your ankles or feet
- sudden weight gain
- fast heartbeat or pounding in your chest

- **Secondary Acute Myeloid Leukemia (AML) (cancer of white blood cells).** A group of anticancer medicines (topoisomerase II inhibitors), including mitoxantrone, may cause the following diseases when used alone but especially in combination with other chemotherapy and/or radiotherapy:
  - cancer of white blood cells (acute myeloid leukemia, AML)
  - a bone marrow disorder that causes abnormally shaped blood cells and leads to leukemia (myelodysplastic syndrome)

Receiving mitoxantrone increases your risk of AML. AML is a cancer of the blood forming cells of your bone marrow. Symptoms of AML can include:

- feeling unusually tired and weak
- increased infections
- bruising and bleeding easily
- fever
- pain in your bones
- trouble breathing
- unexplained weight loss
- night sweats

Blood tests prior and during treatment with mitoxantrone

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Mitoxantrone may affect your blood cell counts. Before you start mitoxantrone and during treatment, your doctor will do a blood test to count the number of your blood cells. Your doctor will carry out blood tests more often, in which he will in particular monitor the number of white blood cells (neutrophilic leucocytes) in the blood:

- if you have a low count of a specific type of white blood cells (neutrophils) (less than 1,500 cells/mm3);
- if you use mitoxantrone in high doses (>14 mg/m2 per day x 3 days).

Heart function tests prior and during treatment with Mitoxantrone

Mitoxantrone may damage your heart and cause deterioration of your heart function or in more severe cases heart failure. You are more prone to these side effects if you take higher doses of mitoxantrone or:

- if your heart is not working well;
- if you had prior treatment of the chest with radiation;
- if you already use other medicines that affect your heart;
- if you had previous therapies with anthracyclines or anthracenediones, such as daunorubicin or doxorubicin.

Before receiving mitoxantrone for the first time, you should have the following tests done:

- physical examination
- a test to check your heart's electrical activity (electrocardiogram)
- a test to check your heart's ability to pump blood

Your doctor will test your heart function before the start of therapy, prior to each subsequent dose and yearly for up to 5 years after the end of therapy.

What is mitoxantrone?

Mitoxantrone is a prescription medicine used alone or with other medicines to treat people with

- breast cancer that spreads to other sites in body
- non Hodgkin's lymphoma (a type of white blood cell cancer)
- adult acute non-lymphocytic leukemia (a cancer of the of blood cells, characterized by the rapid growth of abnormal white blood cells that interfere with the production of normal blood cells)
- highly active relapsing multiple sclerosis (MS) associated with rapidly evolving disability where no alternative therapeutic options exist.

It is not known if mitoxantrone is safe and effective in children.

Who should not receive mitoxantrone?

Do not receive mitoxantrone if you are allergic to mitoxantrone or any of the ingredients in mitoxantrone. See the end of this Medication Guide for a complete list of ingredients in mitoxantrone.

Pregnant and breast-feeding women should also not take mitoxantrone.

What should I tell my doctor before receiving mitoxantrone?

Before you receive mitoxantrone, tell your doctor if you have:

- received mitoxantrone in the past
- heart problems
- liver problems
- kidney problems
- low blood cell counts
- an infection
- had radiation treatment in your chest area
- any other medical conditions

- **are pregnant or plan to become pregnant.** Mitoxantrone may harm your unborn baby. Women who are able to become pregnant should use effective birth control (contraception) while using mitoxantrone and should have a pregnancy test, with known results, before receiving each dose of mitoxantrone. Talk to your doctor about using effective birth control while you receive mitoxantrone.
- **are breast-feeding or plan to breast-feed.** Mitoxantrone can pass into your breastmilk and may harm your baby. Talk to your doctor about the best way to feed your baby if you receive mitoxantrone. Do not breast-feed while receiving mitoxantrone.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.
Using mitoxantrone with certain other medicines may cause serious side effects.

Especially tell your doctor if you take or have taken:

- medicines for cancer treatment called anthracyclines or anthracenediones
- medicines that may affect your heart

Ask your doctor or pharmacist for a list of these medicines if you are not sure if you take or have taken any of these medicines.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I receive mitoxantrone?

- Mitoxantrone is given by slow infusion through a needle placed in a vein (intravenous infusion) in your arm.
- Your doctor will tell you how often you will receive mitoxantrone.
- Your doctor should check how well your heart is working before each mitoxantrone dose. Talk to your doctor if you have not had your heart tests done before your mitoxantrone dose.
- Your doctor will do blood tests during your treatment with mitoxantrone to check your blood cell counts.
- If you are a woman of childbearing age taking mitoxantrone, your doctor should do a pregnancy test before each mitoxantrone dose, even if you are using birth control.
- There is a limit to the total amount of mitoxantrone you can receive during your lifetime. There is a higher risk of heart failure with increasing total lifetime doses of mitoxantrone.

What are the possible side effects of mitoxantrone?

Mitoxantrone may cause some serious side effects. If any of the following happen, tell the doctor immediately:

- If your skin becomes pale and you feel weak or experience sudden shortness of breath, this can be sign of a reduction in red blood cells.
- Unusual bruising or bleeding, such as coughing up blood, blood in your vomit or urine, or black stools (potential sign of platelet reduction).
- New or worsening breathing difficulties.
- Chest pain, breathlessness, changes in your heartbeat (fast or slow), fluid retention (swelling) in the ankles or legs (potential signs or symptoms of heart problems).
- Severe itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), or if you feel you like you are going to faint, these may be signs of severe allergic reaction.
- Fever or infections.

The most common side effects of mitoxantrone include:

- Infections.
- Low number of red blood cells which can cause a feeling of tiredness and shortness of breath (anemia). You may require a blood transfusion.
- Low number of special white blood cells (neutrophils and leukocytes)
- Nausea (feeling sick).
- Vomiting (being sick).
- Hair loss.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of mitoxantrone. For more information, ask your doctor or pharmacist and refer to Patient Information Leaflet that comes with medicine. Call your doctor for medical advice about side effects.

General information about the safe and effective use of mitoxantrone.

This Medication Guide summarizes the most important information about mitoxantrone. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about mitoxantrone that is written for health professionals.

What are the ingredients in mitoxantrone?

Active ingredient: mitoxantrone hydrochloride Inactive ingredients: glacial acetic acid, sodium acetate trihydrate, sodium chloride, sodium metabisulphite (E223) and water for injections.

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Mitoxantron "Ebewe"®
Important note: Before prescribing, consult full prescribing information.
Presentation: Mitoxantron "Ebewe"® **vial containing 20mg/10ml of Mitoxantron.**
Indications:
Mitoxantron is indicated in the treatment of advanced breast cancer, non-Hodgkin's lymphomas, and adult myeloid leukemia, alone or in combination with other antineoplastic agents.
Dosage & Method of administration:
Relief of painful (involuntary) muscle contractions (spasms)
Adults and Elderly:
Advanced Breast Cancer, Non-Hodgkin's Lymphoma:
Single Agent Dosage: The recommended initial dosage of Mitoxantron used as a single agent is 14mg/m² of body surface area, given as a single intravenous dose which may be repeated at 21 day intervals. A lower initial dosage (12mg/m²) is recommended in patients with inadequate bone marrow reserves e.g. due to prior chemotherapy or poor general condition.
Dosage modification and the timing of subsequent dosing should be determined by clinical judgement depending on the degree and duration of myelosuppression. For subsequent courses the prior dose can usually be repeated if white blood cell and platelet counts have returned to normal levels after 21 days.
The following table is suggested as a guide to dosage adjustment, in the treatment of advanced breast cancer and non-Hodgkin's lymphoma according to hematological nadir (which usually occurs about 10 days after dosing).

Nadir after prior dose				
WBC (per mm3)		Platelets (per mm3)	Time to recovery	Subsequent dose after adequate hematological recovery
1,500<	AND	50,000<	days 21≥	Repeat prior dose after recovery, or increase by 2 mg/m2 if myelosuppression is not considered adequate
1,500<	AND	50,000<	days 21<	Withhold until recovery then repeat prior dose
1,500>	OR	50,000>	Any duration	Decrease by 2 mg/m2 from prior dose after recovery
1,000>	OR	25,000>	Any duration	Decrease by 4 mg/m2 from prior

Combination Therapy: Mitoxantron has been given as part of combination therapy. In advanced breast cancer, combinations of
Mitoxantron with other cytotoxic agents including cyclophosphamide and 5-fluorouracil or methotrexate and mitomycin C have been shown to be effective. Reference should be made to the published literature for information on dosage modifications and administration. Mitoxantron has also been used in various combinations for non-Hodgkin's lymphoma, however data are presently limited and specific regimens cannot be recommended.
As a guide, when Mitoxantron is used in combination chemotherapy with another myelosuppressive agent, the initial dose of Mitoxantron should be reduced by 2–4mg/m² below the doses recommended for single agent usage; subsequent dosing, as outlined in the table above, depends on the degree and duration of myelosuppression.

Acute Non-Lymphocytic Leukemia (ANLL):
Single Agent Dosage in Relapse: The recommended dosage for remission induction is 12mg/m² of body surface area, given as a single intravenous dose daily for five consecutive days (total of 60mg/m²). In clinical studies with a dosage of 12mg/m² daily for 5 days, patients who achieved a complete remission did so as a result of the first induction course.
Combination Therapy: Mitoxantron has been used in combination regimens for the treatment of ANLL. Most clinical experience has been with Mitoxantron combined with cytosine arabinoside.
This combination has been used successfully for primary treatment of ANLL as well as in relapse.
An effective regimen for induction in previously untreated patients has been Mitoxantron 10–12mg/m² IV for 3 days combined with cytosine arabinoside 100mg/m² IV for 7 days (by continuous infusion).This is followed by second induction and consolidation courses as thought appropriate by the treating clinician. In clinical studies, duration of therapy in induction and consolidation courses with Mitoxantron have been reduced to 2 days and that of cytosine arabinoside to 5 days. However, modification to the above regimen should be carried out by the treating clinician depending on individual patient factors.
Efficacy has also been demonstrated with Mitoxantron in combination with etoposide in patients who had relapsed or who were refractory to primary conventional chemotherapy. The use of Mitoxantron in combination with etoposide as with other cytotoxics may result in greater myelosuppression than with Mitoxantron alone.
Reference should be made to the published literature for information on specific dosage regimens.

Pediatric population
The safety and efficacy of Mitoxantron in pediatric patients have not been established.

Method of administration
For intravenous use only.
Contraindications:
• Hypersensitivity to Mitoxantron. • Not for intrathecal use.

Warnings and precautions:

• **Precautions for use**:
Mitoxantrone should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. As with other similar cytotoxic agents caution should be exercised when handling mitoxantrone.
Regular monitoring of clinical hematological and biochemical parameters must be made during treatment. Full blood counts should be undertaken serially during the course of treatment. Dosage adjustments may be necessary based on these counts.
• Patients with myelosuppression
Mitoxantrone should be used with caution in patients with myelosuppression or poor general condition.
• Cardiac changes:
Cases of functional cardiac changes, including congestive heart failure and decreases in left ventricular ejection fraction have been reported. The majority of these cardiac events have occurred in patients who have had prior treatment with anthracyclines, prior mediastinal/thoracic radiotherapy, or with pre-existing heart disease. It is recommended that patients in these categories are treated with mitoxantrone at full cytotoxic dosage and schedule. However, added caution is required in these patients and careful regular cardiac examinations are recommended from the initiation of treatment.
As experience of prolonged treatment with mitoxantrone is presently limited, it is suggested that cardiac examinations also be performed in patients without identifiable risk factors during therapy exceeding a cumulative dose of 160mg/m².
• Patients with hepatic impairment:
Careful supervision is recommended when treating patients with severe hepatic insufficiency.
• Mutagenicity:
Mitoxantrone is mutagenic in vitro and in vivo in the rat. In the same species there was a possible association between administration of the drug and development of malignant neoplasia. The carcinogenic potential in man is unknown.

There is no experience with the administration of mitoxantrone other than by the intravenous route.
Safety for intrathecal use has not been established.

Pregnancy • Mitoxantrone should not normally be administered to patients who are pregnant or to mothers who are breast feeding.
Breastfeeding • breast feeding should be discontinued before starting treatment with Mitoxantron Because of the potential for serious adverse reactions in infants,

Interactions
Mitoxantrone in combination with other myelosuppressive drugs may increase the myelotoxicity of mitoxantrone and/or that of the concomitant drugs. Topoisomerase II inhibitors, including mitoxantrone, in combination with other antineoplastic agents, have been associated with the development of acute leukemia.

Adverse drug reactions:

Mitoxantrone is clinically well tolerated demonstrating a low overall incidence of adverse events particularly those of a severe, irreversible or life-threatening nature.
In patients with leukemia, the pattern of side effects is generally similar.
Blood and the lymphatic system disorders
Some degree of leukopenia is to be expected following recommended doses of mitoxantrone. With the single dose every 21 days, suppression of WBC count below 1000/mm³ is infrequent; leucopenia is usually transient reaching its nadir at about 10 days after dosing with recovery usually occurring by the 21st day. Thrombocytopenia can occur and anemia occurs less frequently.
Myelosuppression may be more severe and prolonged in patients having had extensive prior chemotherapy or radiotherapy or in debilitated patients.
Topoisomerase II inhibitors, including mitoxantrone, when used concomitantly with other antineoplastic agents and/or radiotherapy, have been associated with the development of leukemia.
Nervous system disorders
Non-specific neurological side effects such as somnolence, confusion, anxiety and mild paranesthesia have been reported very rare.
Cardiac disorders
Cardiovascular effects which have occasionally been of clinical significance, include decreased left ventricular ejection fraction, ECG changes and acute arrhythmia. Congestive heart failure has been reported and has generally responded well to treatment with digitalis and/or diuretics.
In patients with leukemia an increase in the frequency of adverse cardiac events has been observed; the direct role of mitoxantrone in these cases is difficult to assess as most patients had received prior therapy with anthracyclines and since the clinical course in leukemic patients is often complicated by anemia, fever, sepsis and intravenous fluid therapy.
Gastrointestinal disorders
When mitoxantrone is used as a single injection given every 21 days in the treatment of advanced breast cancer and lymphomas, the most commonly encountered side effects are nausea and vomiting, although in the majority of cases these are mild and transient. Anorexia, constipation, diarrhea, gastrointestinal bleeding, stomatitis and mucositis have been reported rarely.

In patients with leukemia stomatitis and mucositis may be increased in frequency and severity.
Hepatobiliary disorders
Increased liver enzyme levels (with occasional reports of severe impairment of hepatic function in patients with leukemia) have been observed rarely.
Skin and subcutaneous tissue disorders
Blue discoloration of skin and nails have been reported occasionally. Nail dystrophy or reversible blue coloration of the sclera may be seen very rarely. Alopecia may occur, but is most frequently of minimal severity and reversible on cessation of therapy.
Tissue necrosis following extravasation has been reported rarely.
Renal and urinary disorders
Mitoxantrone may impart a blue-green coloration to the urine for 24 hours after administration and patients should be advised that this is to be expected.
Elevated serum creatinine and blood urea nitrogen levels have been observed rarely.
Other side effects which have been reported very rarely include:
Allergic reactions (immunosuppression, exanthem, dyspnoea, hypotension, very rare severe cases as anaphylactic shock), amenorrhoea, dispnoea, fatigue and weakness, fever and conjunctivitis.

You can report any problem or adverse events through:
Patient Safety Department Novartis Consulting AG - Saudi Arabia -.
Mobile: +966508035430 or +96545544426
Phone: +996112658100
Fax: +966112658107
Email: adverse.events@novartis.com

Saudi Food and Drug Authority
National Pharmacovigilance and Drug Safety Center
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Or by online: https://ade.sfda.gov.sa

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