Prescriber Guide

Mitoxantron® (Mitoxantrone Hydrochloride)

SANDOZ A Novartis Division

Prescriber Guide

This Guide for Healthcare Provider has been designed to highlight the risk of cardiac function/myocardial toxicity and secondary acute myeloid leukemia associated with use of mitoxantrone in the treatment of multiple sclerosis, as well as the measures that should be taken to mitigate them. It will facilitate your discussion with the patient and will help you to address any questions or concerns the patient may have.

The purpose of this Guide is to minimise the risk of cardiac function/myocardial toxicity and secondary acute myeloid leukemia associated with use of mitoxantrone.

Although this Guide presents important information concerning the risk of cardiac function/myocardial toxicity and secondary acute myeloid leukemia associated with use of mitoxantrone, please consult the Summary of Product Characteristics (SmPC) for full information on mitoxantrone.

Cardiac function changes/myocardial toxicity:

Cases of functional cardiac changes, including congestive heart failure and decreases in left ventricular ejection fraction have been reported either during therapy with mitoxantrone or months to years after termination of therapy. Other cardiovascular effects, which have been of clinical significance, include electrocardiogram (ECG) changes and acute arrhythmia.

Cardiomyopathy has also been reported in rare instances. Cases of ECG anomalies have been reported. Cases of congestive heart failure with left ventricular ejection fraction (LVEF) < 50 % have also been reported.

These cardiac events have occurred most commonly in patients who have had prior treatment with anthracyclines, prior mediastinal/thoracic radiotherapy, or in patients with pre existing heart disease. The concomitant administration of other cardiotoxic drugs may also increase the risk of cardiac toxicity. 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.

In cancer patients, the risk of symptomatic CHF was estimated to be 2.6% for patients receiving up to a cumulative dose of 140 mg/m2.

To mitigate the cardiotoxicity risk with mitoxantrone, prescribers should consider the following:

- All patients should be assessed for cardiac signs and symptoms by history, physical examination, and ECG prior to start of mitoxantrone therapy. During therapy exceeding 160 mg/m2 of mitoxantrone or during extended treatment cardiac monitoring should be performed in patients without identifiable risk factors.
- All patients should have baseline quantitative evaluation of left ventricular ejection fraction (LVEF) using appropriate methodology (ex. Echocardiogram, multi gated radionuclide angiography (MUGA), Magnetic resonance imaging (MRI) etc.).

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Evaluation of the left ventricular ejection fraction (LVEF) by echocardiogram or multiple gated acquisition (MUGA) is recommended prior to administration of the initial dose of mitoxantrone in cancer patients. Cardiac function for cancer patients should be carefully monitored during treatment. LVEF evaluation is recommended at regular intervals and/or if signs or symptoms of congestive heart failure develops. Cardiotoxicity can occur at any time during mitoxantrone therapy, and the risk increases with cumulative dose. Cardiac toxicity with mitoxantrone may occur at lower cumulative doses whether or not cardiac risk factors are present.

Because of the possible danger of cardiac effects in patients previously treated with daunorubicin or doxorubicin, the benefit to risk ratio of mitoxantrone therapy in such patients should be determined before starting therapy.

Acute congestive heart failure may occasionally occur in patients treated with mitoxantrone for acute myeloid leukemia.

Secondary Acute Myeloid Leukemia:

Mitoxantrone therapy in patients with cancer increases the risk of developing secondary acute myeloid leukemia.

There may be an increased risk of leukemia when mitoxantrone is used as adjuvant treatment of non metastatic breast cancer. In the absence of sufficient efficacy data, mitoxantrone must not be used as adjuvant treatment of non metastatic breast cancer.

Topoisomerase II inhibitors, including mitoxantrone hydrochloride, when used concomitantly with other antineoplastic agents (particularly anthracyclines) and/or radiotherapy, have been associated with the development of Acute Myeloid Leukemia (AML). Treatment with mitoxantrone alone has also been associated with an increased risk of development of secondary acute myeloid leukemia.

Fatal cases of AML have been reported with mitoxantrone use.

Because of the risk of development of secondary malignancies, the benefit to risk ratio of mitoxantrone therapy should be determined before starting therapy.

Precautions for use:

Mitoxantrone is an active cytotoxic drug which should be used by clinicians who are familiar with the use of antineoplastic agents and have the facilities for regular monitoring of clinical, hematological and biochemical parameters during and after treatment.

Full blood counts should be undertaken serially during a course of treatment. Dosage adjustments may be necessary based on these counts.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their national reporting requirements.

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.

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
Toll free phone: 8002490000
Fax: +966112057662
E-mail: npc.drug@sfda.gov.sa
Or by online: https://ade.sfda.gov.sa

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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.