

Mitoxantrone

Guide for prescribing physicians

Essential information for risk minimisation in the treatment of patients with highly active relapsing multiple sclerosis associated with rapidly evolving disability where no alternative therapeutic options exist.

Mitoxantrone 2 mg/ml concentrate for solution for infusion

1. Introduction

Mitoxantrone is a synthetic anthracendione, whose immunosuppressive and immunomodulatory properties are the basis for the use of mitoxantrone in active MS, especially for the treatment of rapidly progressive and highly active inflammatory relapsing MS. The treatment must not be initiated in patients who have been previously treated with mitoxantrone.

The aim of this guide is to minimise the mitoxantrone associated risks of cardiotoxicity and haematotoxicity, including treatment-related acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS). Administration of mitoxantrone must be initiated and monitored by a doctor who has experience with administering cytotoxic chemotherapeutic agents for the treatment of MS. The safety and efficacy of mitoxantrone has not been studied after treatment with other disease-modifying therapies.

In order to minimise risks and adverse reactions, the treating physician must observe the recommended screening procedure before starting therapy and perform the recommended checks during and up to 5 years after ending mitoxantrone therapy. It is important that patients understand the risks associated with taking mitoxantrone and comply with the monitoring requirements, even if they are feeling well, and report symptoms early. The training material for medical staff and patients is intended to contribute to raising awareness with regard to some of the serious risks associated with administering mitoxantrone and the recommendations to reduce these risks.

The prescriber should use the accompanying prescribing physician checklist and also provide all patients with the accompanying patient alert card.

Reporting of Adverse Events

Reporting suspected adverse reactions after authorization 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 via HPRC Pharmacovigilance: www.hpra.ie

Any suspected adverse reactions may also be reported to Pfizer Medical Information on 1800 633 363.

This guide was developed as part of a Risk Management Plan (RMP) for prescribing physicians and medical staff working in the care of patients being treated with mitoxantrone. Mitoxantrone is indicated for the treatment of patients with highly active relapsing multiple sclerosis (MS) associated with rapidly developing disability for which no alternative treatment options exist.

Whilst the risks of cardiotoxicity and leukaemia are associated with all mitoxantrone's licensed indications (please refer to SmPC for complete list) they are considered key to the benefit-risk balance for use in MS patients are therefore additional risk minimisation measures in the form of educational materials for prescribers and patients have been developed.

These educational materials are developed and provided to inform healthcare professionals and patients of the risks of cardiotoxicity and leukaemia and related monitoring requirements during and after treatment for multiple sclerosis, with the aim to facilitate treatment initiation decision-making and ensure the risks are adequately minimised.

Please note that this guide does not deal with all adverse reactions that may occur in association with administration of mitoxantrone. A full description of the potential adverse reactions can be found in the Summary of Product Characteristics.

2. Risks associated with administering mitoxantrone

Cardiotoxicity

In patients with MS who have been treated with mitoxantrone changes in cardiac function can occur, which mainly manifest as asymptomatic worsening of LVEF, but in the severest form also as potentially irreversible and fatal congestive heart failure (CHF). Cardiotoxicity can occur at any time during mitoxantrone therapy or even months or years after ending the therapy.

The risk increases with the cumulative dose, but cardiotoxicity can also occur with mitoxantrone at low cumulative doses and regardless of whether cardiac risk factors are present.

The maximum cumulative lifetime dose must not exceed 72 mg/m².

Before starting treatment with mitoxantrone, a careful benefit-risk analysis must be performed, especially with regard to cardiac risk factors.

Risk factors are as follows:

- Active or latent cardiovascular disease
- previous or concomitant radiotherapy in the mediastinal/pericardial area
- previous therapy with other anthracyclines or anthracendiones (e.g. daunorubicin or doxorubicin)
- or co-administration of other cardiotoxic medications can increase the cardiotoxicity risk.

A link with abnormal heart function has also been proven in MS, and patients with a more serious stage of the disease may be vulnerable to more severe and chronic cardiac function disorders during the treatment.

In order to minimise the risk of cardiotoxicity, testing LVEF by echocardiogram or gated equilibrium radionuclide ventriculography (ERNV) is recommended:

- Before administering the initial dose of mitoxantrone and
- Before each dose in MS patients and
- Annually up to 5 years after ending therapy
- Do not exceed the maximum cumulative lifetime dose of 72mg/m²
- Normally, mitoxantrone should not be administered to MS patients with an LVEF of less than 50% or a clinically significant reduction in LVEF

It is important to inform a patient of the potential cardiotoxic risk before starting the mitoxantrone treatment. It must also be explained to the patient about the possible signs and symptoms and that they must be report them immediately at first onset and adhere to the monitoring recommendations.

Signs and symptoms include:

- Shortness of breath
- Fluid accumulation in the ankles and legs
- Cardiac arrhythmia
- Fatigue
- Decreased ability for physical activity

Haematotoxicity: Treatment-related acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS)

Topoisomerase II inhibitors, of which mitoxantrone is one, have been linked to development of AML or MDS when taken alone and also especially in combination with other cancer medications and/or radiotherapy.

The signs and symptoms of AML and MDS are unspecific and generally associated with cytopenia:

- Anaemia – chronic fatigue, shortness of breath, chills, sometimes with pain in the chest
- Neutropenia – increased vulnerability to infection
- Thrombocytopenia – increased vulnerability to bleeding and ecchymosis and subcutaneous haemorrhaging, that can lead to purpura or petechiae

However, it may be that patients have no symptoms.

Due to the risk of developing secondary malignancy, the benefit-risk ratio of mitoxantrone therapy must be determined before starting therapy.

The therapy with mitoxantrone must be accompanied by close and frequent monitoring of haematological and chemical laboratory parameters and frequent patient observation.

A complete blood count, including platelets, must be performed:

- Before administering the initial dose of mitoxantrone,
- 10 days after administration and
- Before each subsequent infusion and
- In the event of signs and symptoms of an infection.
- Mitoxantrone therapy generally should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm³. It is recommended that frequent peripheral blood cell counts are performed on all patients receiving mitoxantrone in order to monitor the occurrence of bone marrow suppression, primarily neutropaenia, which may be severe and result in infection

In the case of MS, the patient must be explained the risk of malignancy and the signs and symptoms of acute leukaemia before starting the mitoxantrone treatment and be told to go and see a doctor at the onset of such symptoms, even after the five-year period has elapsed and to adhere to the monitoring recommendations.

3. How to administer mitoxantrone?

Mitoxantrone is administered slowly as a free-flowing intravenous infusion. mitoxantrone must not be administered subcutaneously, intramuscularly, intra-arterially or by intrathecal injection.

The recommended dose of mitoxantrone is usually 12 mg/m² body surface area, administered as a short (around 5 to 15 minutes) intravenous infusion that can be repeated every 1-3 months.

Patients with MS should normally not receive a cumulative lifetime dose of more than 72 mg/m².

Normally, mitoxantrone should not be administered to MS patients with an LVEF of <50% or a clinically significant reduction in LVEF.

If mitoxantrone is administered repeatedly, the doses must be adjusted according to the extent and duration of bone marrow suppression.

A differential blood count should be performed before administering the first dose of mitoxantrone, 10 days after administration and before each subsequent infusion and in the event of signs and symptoms of infection.

Differential blood count within 21 days of the mitoxantrone infusion

- Signs and symptoms of an infection and differential blood count WHO Grade 3: following dosage 10 mg/m²
- Signs and symptoms of an infection and differential blood count WHO Grade 4: following dosage 8 mg/m²

Differential blood count 7 days prior to the mitoxantrone infusion

- Signs and symptoms of an infection and differential blood count WHO Grade 1: following dosage 9 mg/m²
- Signs and symptoms of an infection and differential blood count WHO Grade 2: following dosage 6 mg/m²
- Signs and symptoms of an infection and differential blood count WHO Grade 3-4: Discontinue therapy

In the event of non-haematological toxicities (WHO Grade 2-3), the following dose must be adjusted to 10 mg/m². In the event of non-haematological toxicities (WHO Grade 4), the treatment must be discontinued.

Mitoxantrone

Further information can be found in the Summary of Product Characteristics for mitoxantrone and on the website: www.medicines.ie

If a prescriber wishes to obtain more copies of these materials, please contact Pfizer Healthcare Ireland on 01-4676500 or by post to 9 Riverwalk, Citywest Business Campus, Dublin 24, Ireland or otherwise, electronic copies of the educational materials are available on www.hpra.ie