MY/SG C275

HA-30-02-671

Baxter

Please read carefully!

# Mitoxantrone Baxter

Active ingredient: Mitoxantrone hydrochloride

**Composition**

1 ml of the solution for injection contains 2.328 mg Mitoxantrone hydrochloride, equivalent to 2 mg Mitoxantrone, as medicinally active ingredient.
Other constituents: Sodium chloride, sodium acetate, acetic acid, water for injection.

**Dosage form and pack sizes available**

1 injection vial containing 10 mg Mitoxantrone in 5 ml injection solution
1 injection vial containing 20 mg Mitoxantrone in 10 ml injection solution
1 injection vial containing 25 mg Mitoxantrone in 12.5 ml injection solution
1 injection vial containing 30 mg Mitoxantrone in 15 ml injection solution

**Cytostatic agent, Anthracenedione-derivative**

**Manufacturer**

Simtra Deutschland GmbH
Kantstrasse 2
D-33790 Halle/Westfalen
Germany

**Therapeutic Indications**

– carcinoma of the breast
– malignant lymphomas
– acute leukaemias
– primary liver cell carcinoma

**Contraindications**

Mitoxantrone Baxter must not be used in case of known hypersensitivity to the active ingredient.

Mitoxantrone Baxter is contraindicated for intraarterial, subcutaneous, intramuscular or intrathecal administration due to associated toxicities (see section Administration and duration of treatment).

Mitoxantrone should not be used in patients with severe hepatic impairment.

Mitoxantrone Baxter is contraindicated during pregnancy and lactation (see section Pregnancy and Lactation).

**Special warnings and special precautions for use**

WARNINGS

Risk factors for mitoxantrone toxicities and their sequalae described here and in other sections may constitute contraindications. In such situations, individual assessment of risk and expected benefits is necessary. Adverse reactions, depending on their severity, may require dosage modification or discontinuation of treatment.

Cardiotoxicity and Use in Patients with Cardiac Disease:

Use with caution in patients with severe cardiovascular disease, as well as patients with prior treatment with anthracyclines and/or prior mediastinal radiotherapy (see section Adverse reactions).

In patients with cardiovascular risk factors or when mitoxantrone is used in combination with other cardiotoxic drugs, treatment should be carefully monitored and dose adjustment may be necessary (see section Interactions with other Drugs).

Close monitoring of cardiac functions is advisable. More pronounced cardiotoxicity is observed after a total cumulative dose of 160 mg mitoxantrone/$m^2$ body surface area (BSA) (in at risk patients: 140 mg/$m^2$ BSA). The cumulative dose at which a patient has a 50% probability of having to discontinue treatment because of cardiotoxicity was estimated to be 182 mg/$m^2$ . Patients with cardiac insufficiency may respond to supportive treatment with digitalis and/or diuretic agents.

Secondary Acute Myelocytic Leukemia:

Secondary acute myelocytic leukemia (therapy related AML or t-AML) has been reported in cancer patients treated with mitoxantrone. The risk is increased when topoisomerase II inhibitors are given in combination with other DNA-damaging antineoplastic agents and/or radiotherapy, if patients have been previously treated with high doses of cytotoxic drugs, or if doses of topoisomerase II inhibitors have been increased.

Genotoxicity and Effects on Fertility:

Mitoxantrone may be genotoxic

Women should not become pregnant during treatment with mitoxantrone and for up to 9 months after treatment (see section pregnancy and lactation).

Men who are treated with mitoxantrone should not father children during treatment and for up to 6 months after treatment with mitoxantrone.

Women and men should use effective methods of contraception during these periods of time.

Patients on mitoxantrone therapy should seek advice on the risk of irreversible infertility.

PRECAUTIONS

Myelosuppression or Other Severe Infections:

A complete blood count must be checked before each administration of mitoxantrone, as well as at least once during each treatment cycle (see section Adverse Reactions)

Mitoxantrone should be administered with caution to patients suffering from myelosuppression and/or pancytopenia or severe infections.

Bone marrow depression can occur during Mitoxantrone treatment even in the therapeutical dose range. In such a case, a drop in the leucocyte count is observed in the first place. In patients who have previously undergone chemotherapy and/or radiation therapy as well as in patients in a generally poor state of health, marked bone marrow depression can occur. The lowest leucocyte count is generally observed between 6 and 15 days after Mitoxantrone administration. Subsequently, the bone marrow recovers and haematological parameters normalise which, as a rule, is completed by 21 days after administration.

Renal Impairment:

Use with caution in patients with severe renal impairment.

Hepatic Impairment:

Liver function parameters must be checked before each administration of mitoxantrone, as well as at least once during each treatment cycle (Refer section adverse reactions).

Dose reduction may be required, dependent on liver function parameters (i.e., bilirubin).

Use in Pediatric Patients:

There have been no studies performed by Baxter Healthcare Corporation in the pediatric population.

Use in Geriatric Patients:

In geriatric patients, monitoring for toxicities and the need for dose adjustment should reflect the higher frequency of decreased hepatic, renal, cardiac, or other organ function, and concomitant diseases or other drug therapy in this population.

Note:

Mitoxantrone Baxter causes a blue-green coloration of the urine for 1 to 2 days after administration (pantyliner).

Mitoxantrone Baxter must not be mixed with other drugs in an infusion solution or in a syringe.

Do not administer mitoxantrone through the same intravenous line as other drugs.

Heparin must not be added to Mitoxantrone solution as precipitation may occur.

**Interactions with other drugs**

Planned co-administration or sequential administration of other substances or treatments that could increase the likelihood or severity of toxic effects (by means of pharmacodynamics or pharmacokinetic interactions) requires careful individual assessment of the expected benefit and the risks. Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.

- Antineoplastic drugs: Combination therapy may result in increased myelotoxic and cardiotoxic effects.
- Cytostatic drugs and/or radiation therapy: Combination therapy has been associated with t-AML and myelodysplastic syndrome.
- Vaccines: The immunosuppressive effects of mitoxantrone can be expected to reduce the response to vaccination. Use of live vaccines may lead to vaccine-induced infection.
- Cyclosporine: Cyclosporine may reduce mitoxantrone clearance rate in patients with AML.

**Pregnancy and lactation:**

- There are no adequate data from the use of mitoxantrone in pregnant women.
- If mitoxantrone is used during pregnancy, or if the patient becomes pregnant during treatment with mitoxantrone, medical consultation about the risk of damaging effects to the embryo associated with the treatment should occur.
- The effects of mitoxantrone can damage the genotype and influence the development of the embryo (see section Special warning and special precaution for use).
- It is unknown if mitoxantrone can cross the placental barrier.
- Breast-feeding should be discontinued before starting treatment with mitoxantrone. Mitoxantrone passes into breast milk and may be harmful to the child.
- In animal studies, mitoxantrone showed no teratogenic or embryotoxic effects, however, it is considered to be potentially teratogenous in humans, due to its mechanism of action by DNA intercalation.

**Effects on ability to drive and use machines**

There is no information on the effects of mitoxantrone on the ability to operate an automobile or other heavy machinery.

**Posology and method of administration**

The dose should be adjusted to each patient carefully.

Unless otherwise prescribed the following dosages are recommended:

*Intravenous application:*

1. Mammary carcinoma, non-Hodgkin's lymphoma, primary liver cell carcinoma.

During monotherapy, a dose of 14 mg Mitoxantrone/$m^2$ body surface area is recommended as the initial dose for the first cycle. This dose can be repeated after 21 days.

In patients with diminished bone marrow reserves as a result of previous radiation and/or chemotherapy or those in a general poor state of health, the initial dose should be reduced to 12 mg/$m^2$ or corresponding to the hematological parameters.

For each repeated application of Mitoxantrone Baxter, the dose has always to be adjusted in accordance with individual patient progress, the extent and duration of myelosuppression.

*The following general recommendations can be given:*

| **Lowest value (nadir) of leucocytes and thrombocytes (as a rule, 6 to 15 days after application)** | **Return to normal** | **Recommended dosage** |
|---|---|---|
| more than 1.5 G/l leucocytes and more than 50 G/l thrombocytes | 21 days or less | As previous dose |
| more than 1.5 G/l leucocytes and more than 50 G/l thrombocytes | More than 21 days | Wait for return to normal, and then as previous dose |
| less than 1.5 G/l leucocytes or less than 50 G/l thrombocytes | Independent of return to normal | Reduction of the previous dose by 2 mg/$m^2$ |
| less than 1.0 G/l leucocytes or less than 25 G/l thrombocytes | Independent of return to normal | Reduction of the previous dose by 4 mg/$m^2$ |

On combination of Mitoxantrone Baxter with other myelotoxic acting cytostatic agents, it is advisable to reduce the initial dose recommended in case of monotherapy by 2 to 4 mg Mitoxantrone/$m^2$ body surface area. In further treatment cycles, the Mitoxantrone dose should be likewise tailored to individual progress or to the duration and degree of myelosuppression.

2. Acute leukemia's

For the induction treatment of acute leukemia in adults, it is recommended that a daily dose of 10 to 12 mg Mitoxantrone/$m^2$ body surface area is applied for five consecutive days (total dose 50 to 60 mg Mitoxantrone/$m^2$). Higher remission rates can be achieved after a daily dose of 12 mg/$m^2$ for five days. The higher dosage, however, should only be administered when the condition of the patient permits.

By combined use of Mitoxantrone Baxter with other cytostatic agents, dose modifications may be required depending on the condition of the patient. This must be taken into consideration either in the first induction course and/or in subsequent treatment courses.

If severe or life-threatening non-hematological side effects occur even during the first induction course, a second course of treatment should only be begun after these side effects have subsided.

*Intrapleural instillation (e.g. to pleural metastases in cases of breast cancer and non-Hodgkin's lymphoma):*

A single dose of 20 to 30 mg Mitoxantrone is recommended for intrapleural instillation. Any pleural exudate should be drained off as far as possible before therapy. The retention time of this first Mitoxantrone dose in the pleural cavity is 48 hours.

The patients should be kept in a non-resting state during this period in order to achieve a good intrapleural distribution of the cytostatic agent.

After these 48 hours, further drainage of any exudate is carried out. The first treatment cycle is terminated if the volume of the drained exudate is less than 200 ml. If the volume is greater than 200 ml, a further instillation of 30 mg Mitoxantrone is given. Before this second application, the haematological parameters must be checked. The second intrapleural Mitoxantrone dose can be left in place. The maximum dose for one treatment cycle is 60 mg Mitoxantrone.

If the blood leucocyte and platelet counts show normal values after 4 weeks, the intrapleural instillation can be repeated.

Systemic therapy with cytostatic agents should be avoided for 4 weeks before and after intrapleural Mitoxantrone application.

**Administration and duration of treatment**

The application of Mitoxantrone Baxter should only be carried out by a physician specializing in oncology.

Dosage must be individualized.

Doses and duration of treatment and/or treatment intervals depend on the therapeutic indication, the scheme of a combination therapy, the patient's general state of health, organ function, and the results of laboratory monitoring.

Dose reduction depends on hematological parameters such as leukocyte and thrombocyte count.

*Intravenous application:*

Mitoxantrone should be administered slowly as an intravenous infusion over a period of 15-30 minutes (not less than 5 minutes).

Mitoxantrone Baxter is ideally injected slowly into a well-running intravenous infusion system. Isotonic saline or a 5% glucose solution are suitable carrier solutions.

The calculated dose should be diluted with 50 to 100 ml of one of the above mentioned infusion solutions.

If a paravenous infiltration occurs, the application should be immediately stopped and restarted using a different point of entry to the vein.

Isolated cases of severe local reactions (necroses) have been described due to inadvertent paravenous injection.

*Intrapleural instillation:*

For intrapleural instillation, Mitoxantrone Baxter is diluted with isotonic sodium chloride solution.

The Mitoxantrone containing solution must be warmed to body temperature and instilled very slowly (from 5 to 10 min), avoiding any noticeable injection pressure.

*Duration of treatment*

When a cumulative total dose of 200 mg Mitoxantrone/m2 body surface area has been given, the administration of Mitoxantrone Baxter is to be stopped for all indications.

**Special precautions for safe use/handling**

When handling Mitoxantrone Baxter, contamination should be avoided (wear protective gloves and safety goggles). After contact of Mitoxantrone Baxter with the skin or mucous membranes, the contact area should be immediately copiously washed with warm water (not hot). The eyes must be thoroughly rinsed with water.

If necessary, an ophthalmologist should be consulted. In the course of preparation, application and disposal of contaminated material as well as the decontamination of objects (e.g. sanitary facilities), protective gloves and safety goggles must always be worn. Objects, which have been in contact with Mitoxantrone containing solutions, can be cleaned with a suspension of 5.5 parts by weight of calcium hypochlorite in 13 parts of water. They should be copiously rinsed with water. Objects which were detoxificated with hypochlorite inside are to be reused as containers for Mitoxantrone solutions only after rinsing with diluted acetic acid and subsequent repeated rinsing with water.

**Overdose**

In case of acute or chronic overdosage, the observed side effects may be increased, including renal, hepatic and cardiac toxicities (see Adverse Reactions).

If aplasia of the bone marrow occurs as a result of acute overdosage with Mitoxantrone, it may continue for up to 3 weeks.

The extent of bone marrow depression and thrombocytopenia, will determine the further course in acute and chronic overdose. To counteract agranulocytosis and thrombocytopenia, granulocyte colony-stimulating factor and thrombocyte concentrates may be necessary.

There is no specific antidote for mitoxantrone overdose. Emergency procedures should include appropriate corrective and supportive measures.

Mitoxantrone is rapidly eliminated from the blood plasma and shows high tissue affinity; therefore it cannot be eliminated by dialysis.

infection prophylaxis with antibiotics should be considered

Each overdose requires careful monitoring to identify as early as possible, any delayed complications.

**Adverse Reactions**

INFECTIONS AND INFESTATIONS: Sepsis, Infection

NEOPLASM BENIGN AND MALIGNANT (INCLUDING CYSTS AND POLYPS): Acute myeloid leukemia, Myelodysplastic syndrome

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Bone marrow failure, Pancytopenia, Thrombocytopenia, Febrile neutropenia, Neutropenia, Leukopenia, Anemia

IMMUNE SYSTEM DISORDERS: Hypersensitivity reactions

METABOLISM AND NUTRITION DISORDERS: Tumor lysis syndrome

PSYCHIATRIC DISORDERS: Confusional state

CARDIAC DISORDERS: Cardiomyopathy, Cardiac failure, Left ventricular failure, Myocardial infarction, ECG alterations, Arrhythmia

VASCULAR DISORDERS: Phlebitis

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Interstitial pneumonitis, Dyspnea

GASTROINTESTINAL DISORDERS: Nausea, Vomiting, Stomatitis, Abdominal pain, Abdominal tenderness, Diarrhea, Loss of appetite, Constipation, Gastrointestinal bleeding

HEPATOBILIARY DISORDERS: Hepatotoxicity

SKIN AND SUBCUTANEOUS TISSUE DISORDER: Alopecia, Nail disorder, Reversible blue colouration of the sclera, veins and paravenous tissue as well as the nails, Onycholysis including nail discoloration

PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS: Fetal growth restriction

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: Amenorrhea, Oligospermia

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Injection site necrosis, Injection site discoloration, Injection site erythema, Injection site pain, Injection site warmth, Asthenia, Chest pain, Mucosal inflammation, Pain, Pyrexia

INVESTIGATIONS: Ejection fraction decreased, Hepatic enzyme increased, Blood bilirubin increased, Change in blood urea values

**Treatment in case of adverse reactions**

*Bone marrow depression*

Due to the severity of bone marrow depression, a consequent infection prophylaxis with antibiotics has to be initiated. To counteract agranulocytosis and thrombocytopenia, whole blood transfusions, leucocyte and thrombocyte concentrates are suitable. (Please refer to the section "Posology and method of administration for further information).

*Cardiac adverse reactions*

Patients with cardiac insufficiency generally respond well to a supportive treatment with digitalis and / or diuretic agents.

**Special precaution for storage and stability**

Mitoxantrone Baxter should not be used after the expiry date stated on the package!

Mitoxantrone Baxter, opened injection vials and the ready-to-use Mitoxantrone containing infusion solutions should not be stored above + 25 ºC. The solutions should not be frozen!

*Opening of the injection vial:*

The Mitoxantrone injection solution can be dispensed in portions, as required, for a maximum of 7 days when withdrawn aseptically.

*Ready-to-use Mitoxantrone containing infusion solutions:*

The ready-to-use infusion solution should be used within 2 days. Thereafter, remaining solutions should be discarded.

**Disposal of not used Mitoxantrone-containing solutions and empty vials**

Mitoxantrone containing solutions and empty vials should be disposed separately from other drugs according to each current national legal requirement for special waste.

**Store drugs out of children's reach !**

Mitoxantrone Baxter is available on prescription only.

**Incompatibilities**

Mitoxantrone solution must not be mixed with other drugs in an infusion solution or in a syringe.

Do not administer mitoxantrone through the same intravenous line as other drugs.

**Date of last revision of the text**

April 2026