PRESCRIBING INFORMATION

1. MITOXANTRON "EBEWE"

2 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution for infusion 10 mg/5 ml; 20 mg/10 ml
Concentrate for Solution for Infusion
1 ml contains 2 mg mitoxantrone as mitoxantrone hydrochloride
Excipient with known effect: Sodium
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of advanced breast cancer, non-Hodgkin's lymphomas, acute non-lymphocytic leukaemia palliation of non-resectable primary hepatocellular carcinoma.

Mitoxantrone in combination with corticosteroids is indicated for inital chemotherapy in patients with pain due to advanced hormone-refractory prostate cancer.

For reduction of neurologic disability and/or frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (patients whose neurologic status is significantly abnormal between relapses), for patients 18-55 years old.

4.2 Dosage and Method of Administration

Advanced Breast Cancer, Non-Hodgkin's Lymphoma

Single-Agent Dosage: The recommended initial dosage of mitoxantrone used as a single agent is 14 mg/m^2 of body surface area, given as a single intravenous dose which may be repeated at 21-day intervals. A lower initial dosage (12 mg/m^2) 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 haematological nadir (which usually occurs about 10 days after dosing).

Nadir After Prior Dose

WBC (per mm^3)	Platelets (per mm^3)	Time to recovery	Subsequent dose after adequate haematological recovery
>1,500	AND >50,000	≤21 days	Repeat prior dose after recovery, or increase by 2 mg/m^2 if myelosuppression is not considered adequate
>1,500	AND >50,000	>21 days	Withhold until recovery, then repeat prior dose
<1,500	OR <50,000	Any duration	Decrease by 2 mg/m^2 from prior dose after recovery

Combination Therapy: Mitoxantrone has been given as part of combination therapy. In advanced breast cancer, combinations of mitoxantrone 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. Mitoxantrone 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 mitoxantrone is used in combination chemotherapy with another myelosuppressive agent, the initial dose of mitoxantrone should be reduced by 2-4 mg/m^2 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 Myeloid Leukaemia

Single-Agent Dosage in Relapse: The recommended dosage for remission induction is 12 mg/m^2 of body surface area, given as a single intravenous dose daily for five consecutive days (total of 60 mg/m^2). In clinical studies with a dosage of 12 mg mitoxantrone/m^2 daily for 5 days, patients who achieved a complete remission did so as a result of the first induction course.

Combination Therapy: Mitoxantrone has been used in combination regimens for the treatment of acute non-lymphocytic leukaemia (ANLL). Most clinical experience has been with mitoxantrone 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 mitoxantrone 10-12 mg/m^2 IV for 3 days combined with cytosine arabinoside 100 mg/m^2 IV for 7 days (by a 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 mitoxantrone has been reduced to 2 days and that of cytosine arabinoside to 5 days. However, modification of the above regimen should be carried out by the treating clinician depending on individual patient factors.

If severe or life-threatening non-haematological toxicity is observed during the first induction course, the second induction course should be withheld until the toxicity clears.

Reference should be made to the published literature for information on specific dosage regimens.

Children

As experience with mitoxantrone in paediatric leukaemia is limited, dosage recommendations in this patient population cannot be given at present.

Hormone-Refractory Prostate Cancer

Based on the data from two Phase III comparative trials of mitoxantrone plus corticosteroids versus corticosteroids alone, the recommended dosage of mitoxantrone is 12 to 14 mg/m^2 given as a short intravenous infusion every 21 days.

Multiple Sclerosis

The recommended dosage of mitoxantrone hydrochloride is 12 mg/m^2 body surface area given as a short (approx. 5-15 minutes) intravenous infusion every 3 months.

Evaluation of the left ventricular ejection fraction (LVEF) (by echocardiogram or MUGA) is recommended prior to administration of the initial dose of mitoxantrone hydrochloride (see Special Warnings and Precautions for Use).

Complete blood counts, including platelets, should be monitored prior to each course of mitoxantrone hydrochloride and in the event that signs or symptoms of infection develop (see Special Warnings and Precautions for Use).

Women with multiple sclerosis who are biologically capable of becoming pregnant should have a pregnancy test, even if they are using birth control, and the results should be known before receiving each dose of mitoxantrone hydrochloride.

4.3 Contraindications

- Hypersensitivity to the active substance, other anthracyclines or any of its components.
- Mitoxantrone must not be administered intra-arterially, subcutaneously, intramuscularly or intrathecally.
- Use in patients with profound bone marrow suppression is a relative contraindication depending on the clinical circumstances.
- Should not be used during pregnancy and lactation (see section 4.6).

4.4 Special Warnings and Precautions for Use

There may be an increased risk of leukaemia 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.

Mitoxantrone should be used with caution in patients with myelosuppression or poor general condition.

Cases of functional cardiac changes, including congestive heart failure and decreases in left ventricular ejection fraction have been reported during mitoxantrone therapy (see 4.8 Undesirable Effects). 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.

Cardiac monitoring should also be performed in patients without identifiable risk factors during therapy exceeding 160 mg/m^2 of mitoxantrone, or during extended treatment.

Careful supervision is recommended when treating patients with hepatic insufficiency.

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 Leukaemia (AML) or Myelodysplastic Syndrome (MDS). Treatment with mitoxantrone alone has also been associated with an increased risk of development of secondary acute myeloid leukaemia (see 4.8 Undesirable Effects).

Sulphites can cause allergic-type reactions including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma or allergy.

Immunisation may be ineffective when given during mitoxantrone therapy. Immunisation with live virus vaccines are generally not recommended.

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

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, haematological 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 (see Dosage and Method of Administration section).

Mitoxantrone may only be used by a physician with experience in oncology.

Mitoxantrone may only be used by a physician with experience in the treatment of multiple sclerosis.

4.5 Interactions with Other Medicaments and Other Forms of Interaction

Animal data suggest that if used in combination with other antineoplastic agents, additive myelosuppression may be expected. This has been supported by available clinical data on combination regimens. When used in combination regimens, the initial dose of mitoxantrone should be reduced by 2-4 mg/m^2 below the dose recommended for single-agent usage (see Dosage and Method of Administration).

Combining mitoxantrone with potentially cardiotoxic drugs (anthracyclines) increases the risk of cardiac toxicity. The product must be used with caution in combination with immunosuppressive chemotherapy.

4.6 Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women. Mitoxantrone should not normally be administered to patients who are pregnant. If the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be advised of the potential hazard to the foetus. Women of childbearing potential and their partners should be advised to avoid becoming pregnant and use effective contraception during therapy and for at least six months after cessation of therapy.

Mitoxantrone is excreted in human milk and significant concentrations (18 ng/ml) have been reported for 28 days after the last administration. Because of the potential for serious adverse reactions in infants from mitoxantrone, breast-feeding should be discontinued before starting treatment.

4.7 Effects on Ability to Drive and Use Machines

Because of the possible side effects, mitoxantrone can influence the ability to drive and use machines.

4.8 Undesirable Effects

Serious or Life-Threatening Reactions:

Blood and lymphatic system disorders: Some degree of leucopenia is to be expected following recommended doses of mitoxantrone. With the single dose every 21 days, suppression of WBC count below 1000/mm^3 is infrequent. Leucopenia is usually transient, reaching its nadir at about 10 days after dosing with recovery usually occurring by the 21st day. Thrombocytopenia and anaemia occur less frequently. Myelosuppression may be more severe and prolonged in patients who have had extensive prior chemotherapy or radiotherapy or in debilitated patients.

Cardiac disorders: Congestive heart failure may occur during therapy with mitoxantrone, or months to years after the end of treatment (see 4.4 Special Warnings and Precautions for Use). Some cases have been fatal. Treatment with digoxin and/or diuretics has been reported to be effective.

Other cardiovascular effects which have been of clinical significance include decreased left ventricular ejection fraction, ECG changes and acute arrhythmia.

In patients with leukaemia an increase in the frequency of adverse cardiac events has been observed. The direct role of mitoxantrone in these cases is difficult to assess, since some patients had received prior therapy with anthracyclines and since the clinical course in leukaemic patients is frequently complicated by anaemia, fever, sepsis and intravenous fluid therapy. Cardiomyopathy has been reported in rare instances.

Other Undesirable Effects:

Hepato-biliary disorders and renal and urinary disorders: Mitoxantrone Sterile Concentrate may impart a blue-green colouration to the urine for 24 hours after administration, and patients should be advised to expect this during active therapy. Increased liver enzyme levels (with occasional reports of severe impairment of hepatic function in patients with leukaemia). Hyperuricaemia has also been reported. Elevated serum creatinine and blood urea nitrogen levels have been reported.

Skin and subcutaneous tissue disorders: Rash, onycholysis, blue discolouration of skin and nails and nail dystrophy have been reported occasionally. Alopecia may occur, but is most frequently of minimal severity and reversible on cessation of therapy.

Eye disorders: Reversible blue colouration of the sclerae has been reported. Conjunctivitis.

Respiratory disorders: Dyspnoea.

Gastrointestinal disorders: Diarrhoea, anorexia, constipation, gastrointestinal bleeding, abdominal pain, stomatitis and mucositis. The most commonly encountered side effects are nausea and vomiting, although in the majority of cases these are mild and transient.

Neoplasms: Secondary acute myeloid leukaemia (see 4.4 Special Warnings and Precautions for Use).

General disorders and administration site conditions: Fever, fatigue and weakness.

Extravasation at the infusion site has been reported, which may result in erythema, swelling, pain, burning and/or blue discolouration of the skin. Extravasation can result in tissue necrosis with resultant need for debridement and skin grafting. Phlebitis has also been reported at the site of infusion.

Nervous system disorders: Altered taste. Non-specific neurological side effects such as somnolence and mild paraesthesia have been reported.

Metabolism and nutrition disorders: Tumour lysis syndrome (characterised by hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia) has been observed rarely during single-agent chemotherapy with mitoxantrone, as well as during combination chemotherapy.

Psychiatric disorders: Confusion, anxiety.

Reproductive system and breast disorders: Amenorrhoea.

In patients with leukaemia, the pattern of side effects is generally similar, although there is an increase in both frequency and severity, particularly of stomatitis and mucositis. Nevertheless, overall, patients with leukaemia tolerate treatment with mitoxantrone well.

Immune system disorders: Allergic reaction.

4.9 Overdose

There is no known specific antidote for Mitoxantrone Sterile Concentrate. Haemopoietic, gastrointestinal, hepatic or renal toxicity may be seen, depending on the dosage given and the physical condition of the patient. In cases of overdosage patients should be monitored closely and management should be symptomatic and supportive.

Fatalities have occurred on rare occasions as a result of severe leucopenia with infection in patients accidentally given single bolus injections of mitoxantrone at over ten times the recommended dosage. Mitoxantrone Sterile Concentrate is extensively tissue-bound and peritoneal dialysis or haemodialysis is unlikely to be effective in managing overdose.

Prophylaxis with antibiotics has to be initiated.

To bypass agranulocytosis and thrombocytopenia, leucocyte and platelet concentrates are suitable.

The usual supportive measures (compensation of fluid and electrolyte balance, monitoring of renal and hepatic function, strict cardiovascular monitoring, etc.) have to be performed during in-patient treatment.

Each overdose requires careful monitoring of the clinical findings in order to detect late complications in time.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Anthracyclines and related compounds.

ATC code: L01D B07

Although its mechanism of action has not been determined, mitoxantrone is a DNA-reactive agent. It has a cytocidal effect on proliferating and non-proliferating cultured human cells, suggesting activity against rapidly proliferating and slow-growing neoplasms.

5.2 Pharmacokinetic Properties

Pharmacokinetic studies in patients following intravenous administration of mitoxantrone demonstrated a triphasic plasma clearance. Distribution to tissues is rapid and extensive. Elimination of the drug is slow, with a mean half-life of 12 days (range 5-18) and persistent tissue concentrations. Similar estimates of half-life were obtained from patients receiving a single dose of mitoxantrone every 21 days and patients dosed on 5 consecutive days every 21 days.

Mitoxantrone is excreted via the renal and hepatobiliary systems. Only 20-32% of the administered dose was excreted within the first five days after dosing (urine 6-11%, faeces 13-25%). Of the material recovered in the urine 65% was unchanged mitoxantrone and the remaining 35% is primarily composed of two inactive metabolites and their glucuronide conjugates. Approximately two-thirds of the excretion occurred during the first day.

5.3 Preclinical Safety Data

Animal pharmacokinetic studies in rats, dogs and monkeys given radiolabelled mitoxantrone indicate rapid, extensive dose proportional distribution into most tissues.

Mitoxantrone does not cross the blood-brain barrier to any appreciable extent. Distribution into testes is relatively low. In pregnant rats the placenta is an effective barrier.

Plasma concentrations decrease rapidly during the first two hours and slowly thereafter. Animal data established biliary excretion as the major route of elimination. In rats, tissue elimination half-life of radioactivity ranged from 20 days to 25 days as compared with plasma half-life of 12 days. Mitoxantrone is not absorbed significantly in animals following oral administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium chloride, sodium acetate, acetic acid, glacial, sodium sulphate, water for injection

6.2 Incompatibilities

Mitoxantrone should not be mixed with heparin in the same infusion since a precipitate may form. Mitoxantrone should not be mixed with other drugs in the same infusion.

6.3 Shelf life

In the intact container: 24 months

Shelf life after dilution:

The maximum storage time for the ready-to-use drug product infusion solution diluted with a 0.9% sodium chloride solution with a concentration of 0.02 to 2 mg/ml is 28 days when stored at 2-8°C.

From a microbiological point of view, the ready-to-use infusion solution should be used immediately. If the preparation is not used immediately, the user shall be responsible for the duration and the conditions of storage. If the ready-to-use preparation is not produced under controlled and validated aseptic conditions, it shall not be stored longer than 24 hours at 2-8°C.

The chemical and physical stability of the ready-to-use preparation for 24 hours at room temperature (20-25°C) has been demonstrated.

6.4 Special Precautions for Storage

Do not store above 25ºC.

6.5 Instructions for Use, Handling and Disposal

Mitoxantron "Ebewe" should be diluted in at least 50 ml of one of the following intravenous infusions: Sodium chloride 0.9% or Glucose 5%. Administer the resulting solution over not less than 3 minutes via the tubing of freely running intravenous infusion of one of the above fluids. Mitoxantrone should not be mixed with other drugs in the same infusion.

Care should be taken to avoid contact of mitoxantrone with the skin, mucous membranes or eyes. Vials should be dispensed in the upright position in order to prevent drops of mitoxantrone collecting in the stopper during preparation and leading to potential aerosolisation of the solution.

If extravasations occur the administration should be stopped immediately and restarted in another vein. The non-vesicant properties of mitoxantrone minimise the possibility of severe local reaction following extravasations.

As with other potentially cytotoxic compounds caution should be exercised when handling mitoxantrone (gloves, mask, overall). Contact with skin and mucous membranes should be avoided.

Spillage Disposal

The following clean-up procedure is recommended if mitoxantrone is spilled on equipment or environmental surfaces. Prepare a 50% solution of fresh concentrated bleach (any recognised proprietary brand containing either sodium or calcium hypochlorite) in water. Wet absorbent tissues in the bleach solution and apply the wetted tissues to the spillage. The spillage is deactivated when the blue colour has been fully discharged. Collect up the tissues with dry tissues. Wash the area with water and soak up the water with dry tissues. Appropriate protective equipment should be worn during the clean-up procedure. All mitoxantrone contaminated items (e.g., syringes, needles, tissues, etc.) should be treated as toxic waste and disposed of accordingly. Incineration is recommended.

Observe guidelines for the handling of cytotoxic drugs.

Concentrate for solution for infusion must not be used undiluted.

- Cytotoxic drugs should be handled only by trained personnel and in a designated area.
- The work surface should be protected by disposable plastic-backed absorbent paper.
- Protective clothing (goggles, gowns and disposable gloves and masks) should be worn by staff handling parenteral mitoxantrone.
- Contact with skin and/or mucous membranes must be avoided.
- Cytotoxic preparations should not be handled by pregnant staff.
- All items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration.
- Any spillage or waste material may be disposed of by incineration.

Presentations

Mitoxantron "EBEWE" 10 mg – vial of 5 ml

Mitoxantron "EBEWE" 20 mg – vial of 10 ml

MANUFACTURER

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LICENSE HOLDER AND IMPORTER

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