**PRESCRIBING INFORMATION**

# Mitoxantron "Ebewe"

2 mg/ml concentrate for solution for infusion

## COMPOSITION

1 vial of 5 ml contains: 10 mg mitoxantrone (as hydrochloride)
1 vial of 10 ml contains: 20 mg mitoxantrone (as hydrochloride)

## CLINICAL PARTICULARS

### Therapeutic Indications

Mitoxantron "Ebewe" is indicated for chemotherapy in patients with advanced breast cancer, non-Hodgkin's lymphoma, adult acute non-lymphocytic leukaemia (ANLL), palliation of non-resectable primary hepatocellular carcinoma.
Mitoxantron "Ebewe" in combination with corticosteroids is indicated as initial chemotherapy for the treatment of patients with pain-related to advanced hormone-refractory prostate cancer.
Mitoxantron "Ebewe" is indicated for reducing neurological disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive-relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurological status is significantly abnormal between relapses) for ages 18-55 years only.
Mitoxantron "Ebewe" is not indicated in the treatment of patients with primary progressive multiple sclerosis.

### 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 |
| **<1,000** | OR <25,000 | Any duration | Decrease by 4 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/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 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 m/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 *Warnings and Precautions*).
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 *Warnings and Precautions*).
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.

### Contraindications

- Hypersensitivity to the ingredients
- Bone marrow depression
- Not for intrathecal use

### Warnings and Precautions

**When mitoxantrone is used in doses indicated for the treatment of leukaemia, severe myelosuppression will occur. Therefore, it is recommended that Mitoxantron "Ebewe" be administered only by physicians experienced in the chemotherapy of this disease. Laboratory and supportive services must be available for haematologic and chemistry monitoring and adjunctive therapies, including antibiotics. Blood and blood products must be available to support patients during the expected period of medullary hypoplasia and severe myelosuppression. Particular care should be given to assuring full haematologic recovery before undertaking consolidation therapy (if this treatment is used) and patients should be monitored closely during this phase.**
Mitoxantrone should only be administered under the strict supervision of a qualified physician who is experienced in the use of antineoplastic therapy. As with other cytotoxic agents, caution should be exercised when handling mitoxantrone.
Regular monitoring of clinical, haematological and biochemical parameters should be performed during treatment. Full blood counts should be undertaken serially during the course of treatment. Dosage adjustments may be necessary based on these counts.
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. The majority of these cardiac events have occurred in patients who have had prior treatment with anthracycline derivatives, prior mediastinal/thoracic radiotherapy, or with preexisting heart disease. It is recommended that patients in these categories be 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 160 mg/m$^2$.
Careful supervision is recommended when treating patients with severe hepatic insufficiency.
Sulphite may cause allergic reactions including anaphylactic symptoms and bronchospasm in predisposed individuals, especially patients with a prehistory of asthma or allergy.
Mitoxantrone may colour the urine blue-green for up to 24 hours after administration and the patient should be informed hereof. Very rarely, a reversible blue colouring of sclerae may occur.
Immunization may be ineffective when given during mitoxantrone therapy. Immunization with live-virus vaccines is generally not recommended.
Systemic infections should be treated concomitantly with or just prior to commencing therapy with mitoxantrone.
Hyperuricaemia may occur as a result of the rapid lysis of tumour cells by mitoxantrone. Serum urate should be monitored and at hyperuricaemia, treatment should be initiated before initiation of treatment of leukaemia.
Systemic infections should be treated concomitantly or immediately before initiation of treatment with mitoxantrone.
There is no experience with the administration of mitoxantrone other than by the intravenous route.
It must never be given subcutaneously, intramuscularly or intra-arterially. Severe local tissue damage may occur if there is extravasation during administration.
**Not for intrathecal use. Mitoxantrone HCl must not be given by intrathecal injection.**
Severe injury with permanent sequelae can result from intrathecal administration.
Functional cardiac changes may occur in patients with multiple sclerosis treated with mitoxantrone HCl. In one controlled trial, two patients (2%) of 127 receiving mitoxantrone HCl, one receiving a 5-mg/m$^2$ dose and the other receiving the 12-mg/m$^2$ dose, had LVEF values that decreased to below 50%. An additional patient receiving 12 mg/m$^2$, who did not have LVEF measured, had a decrease in another echocardiographic measurement of ventricular function (fractional shortening) that led to discontinuation from the trial. There were no reports of congestive heart failure in either controlled trial.
Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with mitoxantrone HCl or months to years after termination of therapy. Use of mitoxantrone HCl has been associated with cardiotoxicity; this risk increases with cumulative dose. In cancer patients, symptomatic congestive heart failure (CHF) is known to occur in patients receiving up to a cumulative dose of 140 mg/m$^2$. For this reason, patients should be monitored for evidence of cardiac toxicity and questioned about symptoms of heart failure prior to initiation of treatment. Patients with multiple sclerosis who reach a cumulative dose of 100 mg/m$^2$ should be monitored for evidence of cardiac toxicity prior to each subsequent dose. Ordinarily, patients with multiple sclerosis should not receive a cumulative dose greater than 140 mg/m$^2$. Active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with mitoxantrone HCl may occur at lower cumulative doses whether or not cardiac risk factors are present. Except for the treatment of acute nonlymphocytic leukaemia, mitoxantrone HCl therapy generally should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm$^3$. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed in all patients receiving mitoxantrone HCl.
Evaluation of the left-ventricular ejection fraction (LVEF) (by echocardiogram or MUGA) is recommended prior to administration of the initial dose of mitoxantrone HCl. Subsequent LVEF evaluations are recommended, if signs or symptoms of congestive heart failure develop, and prior to all doses administered to patients who have received a cumulative dose of >100 mg/m$^2$. Mitoxantrone HCl should not ordinarily be administered to multiple sclerosis patients who have received a cumulative life-time dose of >140 mg/m$^2$, or to those with either LVEF of <50% or a clinically significant reduction in LVEF.

A complete blood count, including platelets, should be obtained prior to each course of mitoxantrone HCl and in the event that signs and symptoms of infection develop. Mitoxantrone HCl generally should not be administered to multiple sclerosis patients with neutrophil counts less than 1500 cells/$mm^3$.
Liver function tests should also be performed prior to each course of therapy. Mitoxantrone HCl therapy is not recommended in multiple sclerosis patients with abnormal liver function tests, because mitoxantrone HCl clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments.
Topoisomerase II inhibitors, including mitoxantrone HCl, when used concomitantly with other antineoplastic agents and/or radiotherapy, have been associated with the development of acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS).

### Interactions with Other Medicaments and Other Forms of Interaction
Mitoxantrone in combination with other myelosuppresive 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 and/or X-ray treatment, have been associated with the development of acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS).

### Pregnancy and Lactation
Mitoxantrone at doses close to the human dose on a mg/$m^2$ basis has resulted in low foetal birth weight and retarded development of the foetal kidney in treated rats. In treated rabbits, an increased incidence of premature delivery was observed at doses close to the human dose on a mg/$m^2$ basis.
Mitoxantrone HCl may cause foetal harm when administered to a pregnant woman.
Women of childbearing potential should be advised to avoid becoming pregnant.
Women with multiple sclerosis who are biologically capable of becoming pregnant should have a pregnancy test prior to each dose, and the results should be known prior to administration of the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to the foetus.
As with other antineoplastic agents, patients and their partners should be advised to avoid conception for at least six months after cessation of therapy. Mitoxantrone should not normally be administered to patients who are pregnant or to mothers who are breastfeeding.
Mitoxantrone is excreted in human milk and significant concentrations have been reported for about one month after the last administration.

### Undesirable Effects
Myelosuppression is a dose-limiting adverse reaction of mitoxantrone. Cardiac function should be monitored in patients who received >160 mg/$m^2$.

Treatment with mitoxantrone may be associated with:
- Cardiomyopathy
- Dyspnoea
- Anaphylaxis/anaphylactoid reactions (including shock)

***Very Common***
Nausea, alopecia, infection, menstrual disorder, stomatitis, amenorrhoea, leukopenia, arrhythmia, gamma-glutamyltranspeptidase (GGT) increased

***Common (>1/100)***
*Circulation:* asymptomatic reduced left-ventricular function and transient ECG changes after long-term treatment
*Gastrointestinal:* vomiting in app. 50% of the patients, stomatitis, diarrhoea, constipation, abdominal pain and anorexia
*CNS:* nonspecific neurological side effects such as somnolence, confusion, anxiety and mild paraesthesia
*General:* urine abnormal, electrocardiogram (ECG) abnormal, rhinitis, granulocytopenia, white blood count (WBC) abnormal

***Less Common***
*General:* allergic reactions, weakness and fever
*Blood:* anaemia
*Circulation:* acute arrhythmia and cardiac insufficiency after long term treatment
*Gastrointestinal:* gastrointestinal bleeding
*Liver:* increased liver enzymes' values
*Respiratory:* dyspnoea
*Genital/Urinary Tract:* increased serum creatinine and increased nitrogen content in plasma, amenorrhoea
*Others:* mucositis

***Rare (<1/1000)***
*Blood:* secondary malignant disease - acute leukaemia
*Skin:* necrosis upon extravasations

Myelosuppression may be more profound and prolonged in patients who previously have received chemotherapy or radiation therapy. Patients who previously have received anthracyclin and/or radiation therapy and who also suffer from underlying cardiovascular disease, have a higher risk of cardiac affection. Cardiomyopathy and anaphylactic/anaphylactoid reactions (incl. shock) have been reported.

### Paediatric Use
Safety and effectiveness in paediatric patients have not been established.

### Overdose
There is no specific antidote for mitoxantrone. Haemopoietic, gastrointestinal, hepatic or renal toxicity may be seen depending on dosage given and the physical condition of the patient. In cases of overdosage the patient should be monitored closely and treatment should be symptomatic and supportive.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic Properties
Mitoxantrone is an anthracenedione derivative which binds to nuclear DNA. The exact mechanism of action has not been fully explored. The drug has a cytotoxic effect on both proliferating and non-proliferating cultured human cells indicating that mitoxantrone is not cell-cycle-specific.
Mitoxantrone is partly cross-resistant to doxorubicin.
Mitoxantrone can be given together with a number of other cytostatics and glucocorticoids. Increased effect on bone marrow function and gastrointestinal mucosa has been seen, but of reversible nature. This can be avoided through adequate dose adjustment. No unexpected or serious adverse reactions have been seen with other concomitant medication.

### 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 comprised of two inactive metabolites and their glucuronide conjugates. Approximately two-thirds were excreted during the first day.

### Preclinical Safety Data
*Carcinogenesis:* Mitoxantrone administered intravenously to rats and mice at 21-day intervals resulted in an increased incidence of fibroma and external auditory canal tumours in rats and hepatocellular adenoma in male mice. The carcinogen potential in humans is unknown.

*Mutagenesis:* Mitoxantrone produced a clastogenic effect *in vivo* and *in vitro* and was mutagenic in bacterial and mammalian test systems.

## PHARMACEUTICAL PARTICULARS

### List of Excipients
Sodium chloride, sodium acetate, acetic acid, sodium sulphate, water for injection

### 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.

### Special Precautions for Storage
Do not store above 25ºC.
Mitoxantrone infusion substance does not contain an antimicrobial preservative. Therefore, in accordance with normal practice, dilutions for infusion should be used or discarded within 24 hours. Mitoxantrone dilutions will maintain potency for 24 hours at room temperature in PVC or glass containers.

### 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 aerosolization 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 personal and in 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
EBEWE Pharma Ges.m.b.H. Nfg.KG, A-4866 Unterach, Austria

### LICENSE HOLDER
Pharmalogic LTD, P.O.B. 43027, Tel–Aviv 61430

### REGISTRATION NUMBER
129 78 30863 00

*The format of this leaflet was determined by the Ministry of Health which also checked and approved its content in January 2004*

SH0204