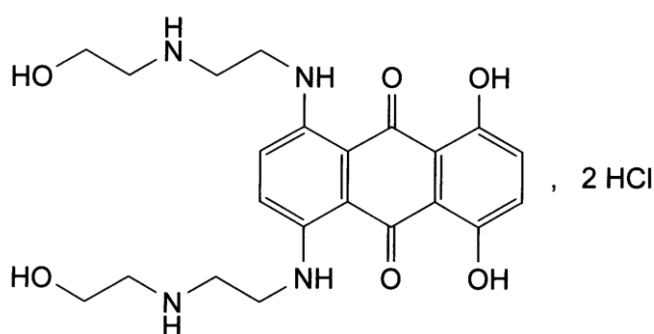


DATA SHEET

MITOZANTRONE EBEWE® 10 MG/5 ML, 20 MG/10 ML INJECTION

NAME OF THE MEDICINE

Mitozantrone (as hydrochloride)



Molecular formula: $C_{22}H_{30}Cl_2N_4O_6$

Molecular weight: 517.4

CAS number: 70476-82-3

DESCRIPTION

Mitozantrone hydrochloride is a hygroscopic dark blue solid, sparingly soluble in water, slightly soluble in methanol, practically insoluble in acetone, acetonitrile or chloroform.

Mitozantrone Ebewe is a sterile, deep blue, aqueous, isotonic solution containing mitozantrone hydrochloride equivalent to 10 mg and 20 mg mitozantrone, sodium chloride, acetic acid, sodium acetate, sodium sulphate and hydrochloric acid in water for injections.

PHARMACOLOGY

Class of medicine

Antineoplastic.

Mode of action

Mitozantrone is a potent cytotoxic synthetic anthracenedione. Although its mechanism of action has not been fully determined, mitozantrone is a DNA-reactive agent. It has a cytotoxic effect on proliferating and nonproliferating cultured human cells. *In vitro* studies suggest that mitozantrone is not cell cycle phase-specific.

In animals, the principal toxic effects of mitozantrone at doses within the human therapeutic range are reversible myelosuppression (manifested predominantly as leucopenia; erythropenia and thrombocytopenia are normally less severe) and lymphocytic depletion of the lymphoid

organs. Gastrointestinal haemorrhage and congestion were noted in continuous daily dosing studies but not in the intermittent schedules to be used clinically.

In dog and monkey studies with mitozantrone, doxorubicin was studied simultaneously at equileucopenic doses as a positive control for anthracycline induced cardiomyopathy. Dogs given mitozantrone and untreated control dogs showed slight dilatation of the sarcoplasmic reticulum which regressed over time. In monkeys, clinical signs of congestive heart failure were observed in animals given doxorubicin, but not mitozantrone. Myocyte alterations in doxorubicin-treated monkeys were characteristic of degeneration, whereas myocyte alterations in monkeys treated with mitozantrone were suggestive of cellular regeneration and repair. In rats, there was no evidence of the progressive cardiomyopathy characteristic of anthracyclines. For an analysis of cardiotoxicity in clinical studies, see **PRECAUTIONS**.

Toxicity studies with mitozantrone in combination with other antineoplastic agents have been carried out in dogs. These studies suggest that additive myelosuppression might be expected in combination therapy.

Efficacy

Clinical studies of efficacy of mitozantrone as a single agent in the treatment of late-stage breast cancer have demonstrated response rates ranging from 20% in previously treated patients to 40% as first-line chemotherapy. Responses have been reported in the primary site and in the following sites of metastases: lymph node, lung, liver, bone and skin.

In a multicentre study of single-agent mitozantrone in the treatment of relapsed or refractory advanced non-Hodgkin's lymphoma, a response rate of 41% was demonstrated, using a dosage schedule of 14mg/m² intravenously every three weeks. The optimal activity of single-agent mitozantrone in relapsed acute non-lymphocytic leukaemia (ANLL) was seen at a dose of 12mg/m², daily for five days. At this dose level a response rate of 39% was observed.

Pharmacokinetics

Following intravenous administration of mitozantrone in patients, a triphasic plasma clearance is observed. The medicine is rapidly and widely distributed into extravascular tissues. Elimination is slow with a terminal half-life of over 12 days (range 5 to 18). Similar estimates of the half-life were obtained from patients receiving mitozantrone on either a schedule of daily for five days or a single dose every three weeks. Plasma accumulation of medicine was not apparent on either schedule.

Mitozantrone is excreted via the renal and hepatobiliary systems. Renal excretion is limited; only 6 to 11% of the dose is recovered in the urine within five days after administration. Of the material recovered in the urine, 65% is unchanged mitozantrone. The remaining 35% comprises primarily two inactive metabolites, the mono and dicarboxylic acid derivatives of mitozantrone and their glucuronide conjugates. One study demonstrated that in the faeces the mean percent recovery of ¹⁴C-labelled material was 18.3% (13.6 to 24.8%) of the administered dose over five days.

In a paper by Batra et al. the protein binding of the drug was quoted as 78% at concentrations ranging from 26 to 455 nanogram ¹⁴C-mitozantrone/mL pooled human plasma. The extent of binding was independent of concentration.

Animal pharmacokinetic studies using radio-labelled mitozantrone indicate rapid, extensive, dose- proportional distribution into most tissues. Biliary excretion is the major route of elimination. The urine and bile of the rat contain the same metabolites that are present in human urine.

No significant difference in the pharmacokinetics of mitozantrone was observed in patients with moderately impaired hepatic function (serum bilirubin 20–60 µmol/L) as compared with 16 patients without hepatic dysfunction. Results of pharmacokinetic studies on 4 patients with severe hepatic dysfunction (bilirubin greater than > 60 µmol/L) suggest that these patients have a lower total body clearance and a larger area under the curve (AUC) than other patients at a comparable mitozantrone dose.

Mitozantrone does not cross the blood brain barrier or the placental barrier. Distribution into testes is relatively low.

Mitozantrone is not absorbed significantly in animals following oral administration.

INDICATIONS

Mitozantrone Ebewe is indicated for the treatment of:

- metastatic carcinoma of the breast
- non-Hodgkin's lymphoma
- adult acute non-lymphocytic leukaemia (ANLL)
- chronic myelogenous leukaemia in blast crisis

CONTRAINDICATIONS

Mitozantrone Ebewe is contraindicated in:

- patients with prior hypersensitivity to mitozantrone
- patients who have received prior substantial anthracycline exposure may not be treated with mitozantrone if cardiac function is abnormal prior to the initiation of therapy (see **PRECAUTIONS**)
- where patients have not recovered from severe myelosuppression due to previous treatment with other cytotoxic agents or radiotherapy
- in patients with severe hepatic impairment

PRECAUTIONS

Mitozantrone Ebewe should be administered only under constant supervision by physicians experienced in therapy with cytotoxic agents and only when potential benefits of mitozantrone therapy outweigh the possible risks. Appropriate facilities should be available for adequate management of complications should they arise.

Full blood counts should be undertaken serially during a course of treatment. Dosage adjustments may be necessary based on these counts (see **DOSAGE AND ADMINISTRATION**).

Systemic infections should be treated concomitantly with, or just prior to, commencing therapy with mitozantrone.

Instructions to Patients

Patients should be instructed to inform their doctor of any prior abnormal heart conditions. Patients should also be advised of the signs and symptoms of myelosuppression.

Patients should be advised to expect a blue/green colouration to the urine for up to 24 hours after mitozantrone administration. Bluish discolouration of the sclera may also occur.

Administration

Mitozantrone is not indicated for subcutaneous, intramuscular, or intra-arterial injection. There have been reports of local/regional neuropathy, some irreversible, following intra-arterial injection.

Mitozantrone must not be given by intrathecal injection. There have been reports of neuropathy and neurotoxicity, both central and peripheral, following intrathecal injection. These reports have included seizures leading to coma and severe neurological sequelae, and paralysis with bowel and bladder dysfunction (see **CONTRAINDICATIONS**).

Haematological

Since mitozantrone produces myelosuppression, it should be used with caution in patients in poor general condition or with pre-existing myelosuppression due to any cause.

There is a high incidence of bone marrow depression, primarily of leucocytes, requiring careful haematological monitoring. Following recommended doses of mitozantrone, leucopenia is usually transient, reaching its nadir at about ten days after dosing, with recovery usually occurring by the twenty-first day. White blood cell counts as low as $1.5 \times 10^9/L$ may be expected following therapy, but white blood cell counts rarely fall below $1.0 \times 10^9/L$ at recommended dosages. Red blood cells and platelets should also be monitored since depression of these elements may also occur. Haematological toxicity may require reduction of dose or suspension or delay of mitozantrone therapy.

Topoisomerase II inhibitors, including mitozantrone, when used concomitantly with other antineoplastic agents and/or radiotherapy, have been associated with the development of Acute Myeloid Leukaemia (AML), Acute Promyelocytic Leukaemia (APL) or Myelodysplastic Syndrome (MDS).

Mitozantrone has been associated with the development of secondary AML in humans (see **ADVERSE EFFECTS**).

Renal Function

Patients with impaired renal failure have not been studied. However, as mitozantrone undergoes limited renal excretion and extensive tissue binding, it is unlikely that the therapeutic effect or toxicity in these patients would be replaced by peritoneal dialysis or haemodialysis.

Cardiovascular

Cases of functional cardiac changes, including congestive heart failure and decreases in left ventricular ejection fraction have been reported during mitozantrone therapy. These cardiac events have occurred most commonly in patients who have had prior treatment with anthracyclines, prior mediastinal radiotherapy or with pre-existing heart disease, indicating a possible increased risk of cardiotoxicity in such patients. It is therefore recommended that regular cardiac monitoring also be performed in these patients, taking into account the extent to which individual patients have been exposed to these cardiac risk factors. A small proportion of endomyocardial biopsy reports have demonstrated changes consistent with anthracycline toxicity in patients who had not received prior anthracyclines. Based on current experience, it is recommended that cardiac monitoring be performed in patients without pre-existing cardiac risk factors before initiation of therapy and during therapy exceeding 140 mg/m^2 of mitozantrone.

Hepatic

Careful supervision is recommended when treating patients with hepatic insufficiency. Although adequate data on the use of mitozantrone in patients with hepatic dysfunction are not yet available, the pharmacokinetic profile suggests that clearance of the drug in such patients may be reduced and dosage may need to be adjusted accordingly. (See **CONTRAINDICATIONS**). Mitozantrone should be used with extreme caution in jaundiced patients.

Uricacidemia

Hyperuricaemia may occur as a result of rapid lysis of tumour cells by mitozantrone. Serum uric acid levels should be monitored and hypouricaemic therapy instituted prior to the initiation of anti-leukaemic therapy.

Carcinogenicity/mutagenicity

Animal studies have not demonstrated teratogenic activity due to mitozantrone treatment. Decreased foetal bodyweight noted in high dose rats (0.2 mg/kg/day) and an increased incidence of premature delivery noted in rabbits (0.01 to 0.05 mg/kg/day) were attributed to maternal toxicity.

Mitozantrone caused point mutations, DNA damage and sister chromatid exchanges *in vitro*. Lifetime studies in mice and rats showed no residual clastogenic effect. Mitozantrone did not induce cell transformation in mammalian neoplasia.

Effects on fertility

The effects of mitozantrone on human fertility have not been established. No adequate studies have been conducted in animals to determine the effect of mitozantrone on fertility.

Use in Pregnancy (Category D)

Category D Medicines which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

There is no information on the use of mitozantrone in pregnancy. Therefore, the medicine should not be used in pregnant women or those likely to become pregnant unless the expected benefits outweigh any potential risks.

Use in lactation

Mitozantrone is excreted in human milk and concentrations of 18 ng/mL have been reported for 28 days following the last administration. Because of potential for serious adverse reactions in infants, breastfeeding should be discontinued before starting treatment with Mitozantrone Ebewe.

Paediatric Use

Experience in paediatric patients is limited.

Interactions with other Medicines

It is recommended that mitozantrone not be mixed in the same infusion with other drugs, as specific compatibility data are not available.

Mitozantrone must not be mixed in the same infusion as heparin as a precipitate may form.

When used in combination regimens, the initial dose of mitozantrone should be reduced by 2 to 4 mg/m² below the dose recommended for single agent usage (see **DOSAGE AND ADMINISTRATION**).

Effects on Laboratory Tests

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 (see *Combination therapy*).

ADVERSE EFFECTS

When used as a single injection every three weeks in the treatment of solid tumours and lymphomas, the most commonly encountered side effects are nausea and vomiting, although in the majority of cases these are mild and transient. Alopecia may occur, but is most frequently of minimal severity and reversible on cessation of therapy.

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

Common reactions:

Gastrointestinal

Nausea, vomiting and stomatitis. In the majority of cases these are mild (WHO Grade 1) and transient.

Dermatological

Alopecia, most frequently of minimal severity and reversible on cessation of therapy.

Haematological:

Myelosuppression, especially leucopenia. Thrombocytopenia and anaemia are less common.

Renal

Mitozantrone may impart a blue-green colouration to the urine for 24 hours after administration.

Less common reactions:

Gastrointestinal

Diarrhoea, anorexia, gastrointestinal bleeding, abdominal pain, altered taste.

Respiratory

Dyspnoea. interstitial pneumonitis.

Local

Phlebitis. Extravasation at the infusion site has been reported, which may result in erythema, swelling, pain, burning and/or blue discolouration of the skin. Tissue necrosis following extravasation has been reported rarely.

General

Allergic reaction (hypotension, urticaria, anaphylaxis) has been reported. Fever, fatigue and weakness, and nonspecific neurological side effects such as somnolence, confusion, anxiety and mild paraesthesia. Tumour lysis syndrome (characterised by hyperuricaemia,

hyperkalaemia, hyperphosphataemia and hypocalcaemia) has been observed rarely during single-agent chemotherapy with mitozantrone, as well as during combination chemotherapy.

Dermatological

Rash, nail pigmentation, onycholysis.

Hepatic

Increased liver enzyme levels and elevated bilirubin levels have been reported occasionally.

Renal

Elevated serum creatinine and blood urea nitrogen levels have been reported occasionally.

Ophthalmic

Reversible blue colouration of the sclerae has been reported.

Severe or life-threatening reactions:

Cardiovascular

Cardiovascular effects include decreased left ventricle ejection fraction (determined by ECHO or MUGA scan), ECG changes and acute arrhythmia. Congestive heart failure has been reported. Such cases have generally responded well to treatment with digitalis and /or diuretics.

Bradycardia, tachycardia and chest pain have been reported.

In patients with leukaemia there is an increase in the frequency of cardiac events. The direct role of mitozantrone in these cases is difficult to assess, since some patients had received prior therapy with anthracyclines, and since their clinical course is frequently complicated by anaemia, fever, sepsis and intravenous fluid therapy.

Haematological

Some degree of leucopenia is to be expected following recommended doses of mitozantrone in solid tumours; however, suppression of white blood cell counts below $1.0 \times 10^9/L$ is infrequent. With dosing every 21 days, leucopenia is usually transient, reaching its nadir at about ten days after dosing, with recovery usually occurring by the twenty-first day. Thrombocytopenia can occur and anaemia occurs less frequently. Myelosuppression may be more severe and prolonged in patients with solid tumours, who have had extensive prior chemotherapy or radiotherapy, or in debilitated patients. Acute Promyelotic Leukemia (APL) has been reported.

Secondary AML/acute myelodysplastic syndrome (AMS) has been reported following chemotherapy with various DNA topoisomerase II poisons, including mitozantrone. In one study a 5% incidence of secondary AML/AMS was reported after treatment with mitozantrone and methotrexate, mitozantrone was suspected as the causative agent. Features of the AML include a latency period of less than three years, short preleukaemic phase and non-specific cytogenic alterations.

DOSAGE AND ADMINISTRATION

Doses greater than 140 mg/m^2 are not recommended, particularly as a single bolus injection. Such administrations have caused fatal overdose as a result of severe leucopenia and infection.

Use in Children

Experience in paediatric patients is limited.

Intrathecal use

Safety for intrathecal use of mitozantrone has not yet been established.

Breast cancer and lymphoma

Single-agent therapy

The recommended initial dosage for use as single agent is 14 mg/m² of body surface area, given as a single intravenous dose, which may be repeated at 21 day intervals. A lower initial dose (12 mg/m² or less) is recommended in patients with inadequate marrow reserves due to prior therapy or poor general condition.

Dosage modification and timing of subsequent dosing should be determined by clinical judgement depending on the degree and duration of myelosuppression. If 21 day white blood cell and platelet counts have returned to adequate levels, prior doses can usually be repeated. The following table indicates a guide to dosing based on myelosuppression for the treatment of breast cancer and non-Hodgkin's lymphoma.

WBC and platelet nadir	Time to recovery	Subsequent dosing
If WBC nadir > 1.5 x 10 ⁹ /L and platelet nadir > 50 x 10 ⁹ /L	Recovery ≤ 21 days	Repeat prior dose or increase by 2mg/m ² if degree of myelosuppression indicates a higher dose can be tolerated
If WBC nadir > 1.5 x 10 ⁹ /L and platelet nadir > 50 x 10 ⁹ /L	Recovery > 21 days	Withhold subsequent dosing until recovery, then repeat prior dose
If WBC nadir < 1.5 x 10 ⁹ /L or platelet nadir < 50 x 10 ⁹ /L	Any duration	Decrease subsequent dosing by 2mg/m ² from prior dose after recovery
If WBC nadir < 1.0 x 10 ⁹ /L or platelet nadir < 25 x 10 ⁹ /L	Any duration	Decrease subsequent dose by 4mg/m ² from prior dose after recovery

Combination therapy

Mitozantrone has been given in various combination regimens with the following cytotoxic agents for the treatment of breast cancer and lymphomas:

- Cyclophosphamide
- Fluorouracil
- Vincristine
- Vinblastine
- Bleomycin
- Methotrexate (standard dose or 200 mg/m² with leucovorin rescue)
- Glucocorticoids

As a guide, the initial dose of mitozantrone when used with other myelosuppressive agents should be reduced by 2 to 4 mg/m² below the doses recommended for single agent usage; subsequent dosing depends upon the degree and duration of myelosuppression.

Long-term survival data for non-Hodgkin's lymphoma are as yet inadequate to establish comparability between combinations containing mitozantrone and similar combinations containing doxorubicin.

Leukaemia:

Single agent dosage for patients with acute non-lymphocytic leukaemia or chronic myelogenous leukaemia in blast crisis. Mitozantrone as 'single-agent therapy' is also indicated in the treatment of acute non-lymphocytic leukaemia. The recommended dosage for induction is 12 mg/m² of body surface area, given as a single intravenous dose daily for five consecutive days (total of 60 mg/m²).

In clinical studies, with a dosage of 12 mg/m² daily for five days, patients who achieved a complete remission did so as a result of the first induction course.

Reinduction upon relapse may be attempted with mitozantrone and again the recommended dosage is 12 mg/m² daily for five days.

Combination therapy

Mitozantrone, together with cytosine arabinoside, has been used successfully for the treatment of both first- and second-line patients with acute non-lymphocytic leukaemia.

For induction, the recommended dosage is 10 to 12 mg/m² of mitozantrone for three days and 100 mg/m² of cytosine arabinoside for seven days (the latter given as a continuous 24-hour infusion).

If a second course is indicated, then the second course is recommended with the same combination at the same daily dosage levels but with mitozantrone given for only two days and cytosine arabinoside for only five days.

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.

Directions for use

Mitozantrone Ebewe should be diluted to at least 50 mL with either sodium chloride for injection or 5% glucose for injection. Mitozantrone Ebewe should be introduced slowly into the tube of a freely running intravenous infusion of sodium chloride for injection or 5% glucose for injection over not less than three to five minutes. Follow administration with a flush of the appropriate diluent. If extravasation occurs, the administration should be stopped immediately and restarted in another vein.

Pharmaceutical precautions

Care should be taken to avoid contact of mitozantrone with the skin, mucous membranes or eyes. The use of goggles, gloves and protective gowns is recommended during preparation and administration. To reduce the possibility of spillages and splashes when removing Mitozantrone Ebewe from the vial, it is recommended that a 21 gauge (or 0.8mm internal diameter equivalent) needle be used.

- Mitozantrone can cause staining.
- Skin accidentally exposed to mitozantrone should be rinsed copiously with warm water and if the eyes are involved, standard irrigation techniques should be used. Equipment and spills on environmental surfaces may be cleaned up by using an aqueous solution of calcium hypochlorite (5.5 parts calcium hypochlorite in 13 parts by weight of water for each 1 part by weight of Mitozantrone Ebewe). Absorb the remaining solutions with gauze

or towels and dispose of these in a safe manner. Appropriate safety equipment such as goggles and gloves should be worn while working with calcium hypochlorite solutions.

- Mitozantrone Ebewe does not contain an antimicrobial preservative. Although Mitozantrone Ebewe has demonstrated significant self-preserving qualities, unused proportions of the undiluted solution should be discarded as soon as possible after opening. Following preparation of the infusion, mitozantrone solutions will maintain potency for 72 hours; however, to reduce microbiological hazards, the solution should be used as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C-8°C for not more than 24 hours. Discard any unused portion within 24 hours of preparation. Mitozantrone should **not** be mixed in an infusion containing other medicines.
- Mitozantrone Ebewe is for single use in one patient only. Discard any residue.

Handling precautions

As with all antineoplastic agents, trained personnel should prepare Mitozantrone Ebewe. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn while handling mitozantrone. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as mitozantrone.

Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

Items used to prepare mitozantrone, or articles associated with body waste should be disposed of by placing in a double sealed polythene bag, and incinerating at 1100°C.

Spills and disposal

If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towel or adsorbent granules. Spills may also be treated with 5% sodium hypochlorite. Collect up absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled **CYTOTOXIC WASTE FOR INCINERATION AT 1100°C**. Waste material should be incinerated at 1100°C for at least 1 second. Cleanse the remaining spill area with copious amounts of water.

OVERDOSAGE

Contact the Poisons Information Centre (in Australia, call 131126; in New Zealand call 0800 POISON or 0800 764 766) for advice on management of overdose.

The symptoms of overdose are likely to be an extension of the pharmacological actions of mitozantrone. Possible symptoms of toxicity are those listed under **ADVERSE EFFECTS**. Haematopoietic, gastrointestinal, hepatic or renal toxicity may be seen depending on the dosage given and the physical condition of the patient. Toxicity may be delayed and life threatening (e.g. myelosuppression).

Treatment

There is no known specific antidote for mitozantrone. In cases of overdose the patient should be monitored closely. Haematological support and antimicrobial therapy may be required during prolonged periods of myelosuppression. Management should be symptomatic and supportive.

PRESENTATION AND STORAGE CONDITIONS

Mitozantrone Ebewe 10 mg in 5mL injection, solution - glass vial. Pack of 1 vial.
Mitozantrone Ebewe 20 mg in 10mL injection, solution - glass vial. Pack of 1 vial.

Store below 25°C

MEDICINE CLASSIFICATION

Prescription Medicine (S4)

NAME AND ADDRESS

Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt. Wellington
Auckland
New Zealand

DATE OF PREPARATION

25 Nov 2011