SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

MITOXANTRONE-HEXAL 20 mg/10 mℓ (solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Mitoxantrone-Hexal 20 mg/10 mℓ solution for infusion contains 2,328 mg of mitoxantrone hydrochloride per 1 mℓ of solution.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion (Clear, blue solution, free of particles).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MITOXANTRONE-HEXAL is indicated for chemotherapy:

I. In patients with carcinoma of the breast, including locally advanced or metastatic disease.

II. In patients with non-Hodgkin's lymphoma having the following histology:

Modified Rappaport Classification

1) nodular poorly differentiated lymphocytic

   nodular mixed lymphocytic

2) nodular histiocytic

   diffuse poorly differentiated lymphocytic

diffuse mixed

3) diffuse histiocytic lymphoma.

Patients with indolent lymphomas (group 1) should have failed first line therapy with an alkylating agent or the combination regimen cyclophosphamide, vincristine and prednisone.

Patients with aggressive lymphomas (groups 2 and 3) should have failed first line therapy with the combination regimen cyclophosphamide, vincristine, adriamycin, prednisone with or without bleomycin and methotrexate.

III. In adult acute non-lymphocytic leukaemia at relapse and chronic myelogenous leukaemia in blast crisis.

IV. In combination with low dose oral corticosteroids, MITOXANTRONE-HEXAL is indicated as initial chemotherapy for the symptomatic treatment of patients with intractable pain related to advanced hormone-refractory prostate cancer.

4.2 Posology and method of administration

Posology

MITOXANTRONE-HEXAL should be administered under the supervision of a medical practitioner experienced in the use of cytotoxic chemotherapy agents.

Breast cancer, lymphoma

The recommended initial dosage for use as a single agent is 14 mg/m^2 (body surface area) given as a single intravenous injection. Dose may be repeated at 21 day intervals. A lower initial dose (12 mg/m^2) is recommended in patients with inadequate marrow reserves due to old age, prior therapy or poor general condition.

Modification of these initial doses and the time of subsequent dosing depend of the degree and duration of the myelosuppression. Full doses in subsequent courses can be given if 21 day white blood cell (WBC) and platelet counts have returned to adequate levels.

The following table indicates recommended dosing, based on myelosuppression.

Table 1: Recommended dosage based on myelosuppression

WBC and Platelet nadir	***Time to recovery***	***Subsequent Dosing***
If WBC nadir > 1500 µℓ and platelet nadir > 50 000 µℓ	Recovery ≤ 21 days	Repeat initial dose
If WBC nadir > 1500 µℓ and platelet nadir > 50 000 µℓ	Recovery > 21 days	Withhold until recovery, then repeat full dose
If WBC nadir < 1500 µℓ or platelet nadir < 50 000 µℓ	Any duration	Decrease by 2 mg/m^2 from initial dose
If WBC nadir < 1000 µℓ or platelet nadir < 25 000 µℓ	Any duration	Decrease by 4 mg/m^2 from initial dose

Dosage for patients with acute non-lymphocytic leukaemia in relapse or chronic myelogenous leukaemia in blast crisis

The recommended dosage for induction is 12 mg/m^2 of body surface area, given as a single intravenous dose daily for 5 consecutive days (total of 60 mg/m^2).

Most complete remissions will occur following the initial course of induction therapy. In the event of an incomplete antileukaemic response, a second induction course may be given.

Re-induction upon relapse may be attempted with MITOXANTRONE–HEXAL and again the recommended dosage is 12 mg/m^2 daily for 5 consecutive days.

Long term use of mitoxantrone suggests neither cumulative toxic effects nor progressive depletion of white blood cells. However, experience beyond twelve courses of therapy is limited and careful monitoring of the patient is advised during prolonged treatment.

In the treatment of lymphoma, mitoxantrone has been given in combination regimens with:

- cyclophosphamide
- vincristine
- bleomycin
- methotrexate (standard dose of 200 mg/m^2 with leucovorin rescue)
- glucocorticoids

As a guide, the initial dose of MITOXANTRONE-HEXAL when used with other myelosuppressive medicines should be reduced by 2 to 4 mg/m^2 below the doses recommended for single medicine usage; subsequent dosing depends upon the degree and duration of myelosuppression.

In the treatment of leukaemia, MITOXANTRONE-HEXAL has been used with cytosine arabinoside.

For induction, recommended dosage is 10 to 12 mg/m^2 of MITOXANTRONE-HEXAL for 3 days and 100 mg/m^2 of cytosine arabinoside for 7 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 MITOXANTRONE-HEXAL given for only 2 days and cytosine arabinoside for only 5 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.

Limited experience with MITOXANTRONE-HEXAL in the treatment of paediatric patients with acute leukaemia indicates a maximum tolerated dose of 8 mg/m^2.

Hormone-refractory prostate cancer

The recommended dosage of MITOXANTRONE-HEXAL is 12 to 14 mg/m^2 given as a short intravenous infusion every 21 days in combination with prednisone 10 mg daily.

Cancer patients who received cumulative doses of MITOXANTRONE-HEXAL of 140 mg/m^2 either alone or in combination with other chemotherapeutic agents had a cumulative 2,6 % probability of clinical congestive heart failure. For this reason, patients should be monitored for evidence of cardiac toxicity and questioned about symptoms of heart failure prior to the initiation of and during treatment.

Special populations

Elderly people

In general, dose selection for an elderly patient should be initiated at the low end of the dosing range, reflecting the greater frequency of decreasing hepatic, renal, or cardiac function, and of concomitant disease or treatment with other medicinal products.

Renal impairment

The safety of MITOXANTRONE-HEXAL in patients with renal impairment is not established. MITOXANTRONE-HEXAL should be used with caution.

Hepatic impairment

The safety of MITOXANTRONE-HEXAL in patients with hepatic insufficiency is not established. For patients with hepatic impairment dose adjustment may be necessary as MITOXANTRONE-HEXAL clearance is reduced by hepatic impairment. There are insufficient data that allows for dose adjustment recommendations. Laboratory measurement cannot predict clearance of the active substance and dose adjustments (see section 5.2).

Paediatric population

Safety and efficacy in paediatric patients have not been established. There is no relevant use of MITOXANTRONE-HEXAL in the paediatric population.

4.3 Contraindications

MITOXANTRONE-HEXAL is contraindicated in patients who have demonstrated prior hypersensitivity to mitoxantrone or to any of the excipients, including sulphites that may be produced during the manufacturing of MITOXANTRONE-HEXAL. MITOXANTRONE-HEXAL must not be administered intra-arterially, subcutaneously, intramuscularly or intrathecally (see section 4.4).

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

MITOXANTRONE-HEXAL should be administered under the supervision of a medical practitioner experienced in the use of cytotoxic chemotherapy agents. Precautions to be taken before handling or administering the medicinal product.

MITOXANTRONE-HEXAL should be given slowly into a free flowing intravenous infusion. It must never be given subcutaneously, intramuscularly, or intra-arterially (see section 4.3).

There have been reports of local/regional neuropathy, some irreversible, following intra-arterial injection. Severe tissue damage may occur if there is extravasation during administration. To date, only isolated cases of severe local reactions (necrosis) have been described due to extravasation. The intrathecal use of MITOXANTRONE-HEXAL is contraindicated (see section 4.3). Severe injury with permanent sequelae can result from intrathecal administration. 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 neurologic sequelae, and paralysis with bowel and bladder dysfunction.

Except for the treatment of acute non-lymphocytic leukaemia, MITOXANTRONE-HEXAL therapy generally should not be given to patients with baseline neutrophil count of less than 1500 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 on all patients receiving MITOXANTRONE-HEXAL.

Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with MITOXANTRONE-HEXAL or months to years after termination of therapy. Use of MITOXANTRONE-HEXAL has been associated with cardiotoxicity; this risk increases with cumulative dose.

In cancer patients, the risk of symptomatic congestive heart failure (CHF) was estimated to be 2,6 % for patients receiving up to the 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.

Active or dormant cardiovascular disease, prior to concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic medicines may increase the risk of cardiotoxicity. Evaluation of the left-ventricular ejection fraction (LVEF) by echocardiogram or multiple-gated acquisition (MUGA) is recommended prior to administration of the initial dose of MITOXANTRONE-HEXAL in cancer patients. Cardiac function for cancer patients should be carefully monitored during treatment. LVEF evaluation is recommended at regular intervals and/or if signs or symptoms of congestive heart failure develop.

Cardiotoxicity can occur at any time during MITOXANTRONE-HEXAL therapy, and the risk increases with cumulative dose. Cardiac toxicity with MITOXANTRONE-HEXAL may occur at lower cumulative doses whether or not cardiac risk factors are present.

Secondary acute myelogenous leukaemia (AML) has been reported in cancer patients treated with anthracyclines. MITOXANTRONE-HEXAL is an anthracenedione, a related medicine. The occurrence of refractory secondary leukaemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pre-treated with cytotoxic medicines, or when doses of anthracyclines have been escalated.

The cumulative risk of developing treatment-related AML; in 1774 patients with breast cancer who received mitoxantrone HCl concomitantly with other cytotoxic agents and radiotherapy, was estimated as 1,1 % and 1,6 % at 5 and 10 years, respectively.

Bone marrow suppression

During the treatment, regular monitoring of clinical, haematological and biochemical parameters is necessary, as well as frequent patient observation. A full blood count, including platelets, should be obtained prior to administration of the initial dose of MITOXANTRONE-HEXAL, 10 days following the administration and prior to each subsequent infusion and in the

event that signs and symptoms of infection develop. On the basis of the values obtained, dose adjustments may be necessary (see section 4.2). In the presence of pancytopenia or severe florid infections, caution is advised when using MITOXANRONE-HEXAL.

Patients should be informed about risks, symptoms and signs of acute leukaemia and prompted to seek medical attendance if any such symptoms should occur even after the five year period has passed.

MITOXANTRONE-HEXAL can, regardless of the dose, lead to myelosuppression. Myelosuppression may be more severe and prolonged in patients with poor general condition, or prior chemotherapy and/or radiotherapy.

Except for the treatment of acute myeloid leukaemia, MITOXANTRONE-HEXAL therapy generally should not be given to patients with baseline neutrophil counts of less than 1500 cells/mm^3.

It is recommended that frequent peripheral blood cell counts are performed on all patients receiving MITOXANTRONE-HEXAL in order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection.

When MITOXANTRONE-HEXAL is used in doses (> 14 mg/m^2/d x 3 days) indicated for the treatment of leukaemia, severe myelosuppression will occur. Therefore, it is recommended that MITOXANTRONE-HEXAL be administered only by medical practitioners 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.

Cardiac effects – general

Patients with severe anamnestic cardiopathies should be treated with special caution with MITOXANTRONE-HEXAL and be monitored carefully. This applies especially to patients in whom these diseases were caused by anthracycline pre-treatment or as a result of mediastinal pre-irradiation or in patients with pre-existing cardiovascular disease.

Patients with one or more of these risk factors and if MITOXANTRONE-HEXAL is combined with cardiotoxic cytostatics or other cardiotoxic medicines should be monitored carefully (dose adjustment if necessary) (see boxed section 4.4).

Regular checks of the cardiac function with appropriate methods have to be performed.

Evaluation of the Left-Ventricular Ejection Fraction (LVEF) is recommended prior to administration of the initial dose of MITOXANTRONE-HEXAL. 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.

Functional cardiac changes including decreases in LVEF and irreversible congestive heart failure can occur with MITOXANTRONE-HEXAL.

Cardiac effects – cancer

Cardiotoxicity can occur at any time during MITOXANTRONE-HEXAL therapy, and the risk increases with cumulative dose. Cardiotoxicity with MITOXANTRONE-HEXAL may occur even in the absence of cardiac risk factors at lower cumulative doses (less than 100 mg/m^2). Cancer patients who received cumulative doses of 140 mg/m^2 either alone or in combination with other chemotherapeutic agents had a cumulative 2,6 % probability of clinical congestive heart failure. In comparative oncology trials, the overall cumulative probability rate of moderate or severe decreases in LVEF at this dose was 13 % (see boxed section 4.4).

Because of the possible danger of cardiac effects in patients previously treated with daunorubicin or doxorubicin, the benefit-to-risk ratio of MITOXANTRONE-HEXAL therapy in such patients should be determined before starting therapy.

Acute congestive heart failure may occasionally occur in patients treated with MITOXANTRONE-HEXAL for acute non-lymphocytic leukaemia (see boxed section 4.4).

Functional cardiac changes such as decreases in LVEF and congestive heart failure may occur in patients with hormone-refractory prostate cancer treated with MITOXANTRONE-HEXAL (see boxed section 4.4).

Non-metastatic breast cancer

In the absence of sufficient efficacy data in the adjuvant treatment of breast cancer and accounting for the increased risk of leukaemia, MITOXANTRONE-HEXAL should only be used for metastatic breast cancer.

Infections

Patients who receive immunosuppressive medicines have a reduced immunological response to infection. Systemic infections should be treated concomitantly with or just prior to commencing therapy with MITOXANTRONE-HEXAL.

Vaccination

If patients are treated with immunosuppressive medicines and receive a vaccine concomitantly, it has been shown that patients have minimal antibody response after vaccination. Vaccination with live virus (e.g. yellow fever vaccination) may result in severe reactions such as vaccinia gangrenosa, generalised vaccinia or death. Immunisation may be ineffective when given during MITOXANTRONE-HEXAL therapy. Therefore, immunisations with live virus vaccines are generally not recommended during treatment with MITOXANTRONE-HEXAL. It is advised to use live virus vaccines with caution after stopping

chemotherapy, and vaccinate not sooner than 3 months after the last dose of chemotherapy (see section 4.5).

Contraception in males and females

MITOXANTRONE-HEXAL is genotoxic and is considered a potential human teratogen. Therefore, men under therapy must be advised not to father a child and to use contraceptive measures during and at least 6 months after therapy. Women of childbearing potential should have a negative pregnancy test prior to each dose, and use effective contraception during therapy and for at least 4 months after cessation of therapy (see section 4.3).

Breastfeeding

Mitoxantrone has been detected in breast-milk for up to one month after the last administration. Because of the potential for serious adverse reactions in infants from MITOXANTRONE-HEXAL, breastfeeding is contraindicated (see section 4.3) and must be discontinued before starting treatment.

Fertility

Women of childbearing potential should be informed about increased risk of transitory or persistent amenorrhoea (see section 4.6).

Mutagenicity and carcinogenicity

Mitoxantrone was found to be mutagenic in bacterial and mammalian test systems, as well as *in vivo* in rats. The active substance was carcinogenic in experimental animals at doses below the proposed clinical dose. Therefore, MITOXANTRONE-HEXAL has the potential to be carcinogenic in humans.

Tumour lysis syndrome

Cases of tumour lysis syndrome were reported with the use of MITOXANTRONE-HEXAL. Levels of uric acid, electrolytes and urea should be monitored.

Hepatic insufficiency

The safety of MITOXANTRONE-HEXAL in patients with hepatic insufficiency is not established. MITOXANTRONE-HEXAL therapy in patients with abnormal liver function tests is not recommended because MITOXANTRONE-HEXAL clearance is reduced by hepatic impairment and no laboratory measurement can predict medicine clearance and dose adjustments.

Secondary acute myeloid leukaemia and myelodysplastic syndrome

Topoisomerase II inhibitors, including mitoxantrone hydrochloride, when used concomitantly with other antineoplastic medicines and/or radiotherapy have been associated with the development of Acute Myeloid Leukaemia (AML) or Myelodysplastic Syndrome (MDS). Treatment with MITOXANTRONE-HEXAL alone has also been associated with an increased risk of development of secondary AML.

Because of the risk of development of secondary malignancies, the benefit-to-risk ratio of MITOXANTRONE-HEXAL therapy should be determined before starting therapy.

Sulfites

Sulfites may be produced during the manufacturing of MITOXANTRONE-HEXAL. This product may contain sodium metabisulfite. Sulfites can cause allergic-type reactions including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma or allergy.

Discolouration of urine and other tissues

MITOXANTRONE-HEXAL may impart a blue-green colour to the urine for 24 hours after administration, and patients should be advised to expect this during therapy. Bluish discolouration of the sclera and nails may also occur.

Therapy with MITOXANTRONE-HEXAL should be accompanied by close and frequent monitoring of haematologic and chemical laboratory parameters, as well as frequent patient observation.

A complete blood count, including platelets, should be obtained prior to each course of MITOXANTRONE-HEXAL and in the event that signs and symptoms of infection develop.

MITOXANRONE-HEXAL should be used with caution in patients with severe hepatic or renal insufficiency.

Liver function tests should also be performed prior to each course of therapy. MITOXANTRONE-HEXAL therapy in patients with abnormal liver function tests is not recommended because MITOXANTRONE-HEXAL clearance is reduced by hepatic impairment and no laboratory measurement can predict medicine clearance and dose adjustments.

4.5 Interaction with other medicines and other forms of interaction

In combined treatments with other anti-neoplastic substances, increased toxicity (especially myelotoxicity and cardiotoxicity) cannot be excluded. Combining MITOXANTRONE-HEXAL with potentially cardiotoxic active substances (e.g. anthracyclines) increases the risk of cardiac toxicity.

Topoisomerase II inhibitors, including mitoxantrone hydrochloride, when used concomitantly with other antineoplastic medicines and/or radiotherapy have been associated with the development of Acute Myeloid Leukaemia (AML) or Myelodysplastic Syndrome (MDS) (see section 4.8).

MITOXANTRONE-HEXAL causes myelosuppression as an extension of its pharmacological action. Myelosuppression can be increased when it is used in combination chemotherapy with another myelosuppressive agent such as for treatment of breast cancer.

The combination of MITOXANTRONE-HEXAL with other immunosuppressive agents may increase the risk of excessive immunodepression and lymphoproliferative syndrome.

Immunisation with live virus vaccines (e.g. yellow fever vaccination) increases the risk of infection and other adverse reactions such as vaccinia gangrenosa and generalised vaccinia, in patients with reduced immunocompetence, such as during treatment with MITOXANTRONE-HEXAL. Therefore, live virus vaccines should not be administered during therapy. It is advised to use live virus vaccines with caution after stopping chemotherapy, and vaccinate not sooner than 3 months after the last dose of chemotherapy (see section 4.4).

The combination of vitamin K antagonists and cytotoxic agents may result in an increased risk of bleeding. In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR should be closely monitored with the addition and withdrawal of treatment with MITOXANTRONE-HEXAL and should be reassessed more frequently during concurrent therapy. Adjustments of the anticoagulant dose may be necessary in order to maintain the desired level of anticoagulation.

Mitoxantrone has been demonstrated to be a substrate for the BCRP transporter protein *in vitro*. Inhibitors of the BCRP transporter (e.g. eltrombopag, gefitinib) could result in an increased bioavailability. In a pharmacokinetic study in children with de novo acute myeloid leukaemia, ciclosporin co-medication resulted in a 42 % decreased clearance ofmitoxantrone. Inducers of the BCRP transporter could potentially decrease MITOXANTRONE-HEXAL exposure.

Mitoxantrone and its metabolites are excreted in bile and urine, but it is not known whether the metabolic or excretory pathways are saturable, may be inhibited or induced, or if mitoxantrone and its metabolites undergo enterohepatic circulation (see section 5.2).

Changes in laboratory test values have been observed infrequently e.g. increased liver enzyme levels, elevated serum creatinine and blood urea.

Compatibility with other therapeutic agents

MITOXANTRONE-HEXAL must not be mixed in the same infusion as heparin since a precipitate may form. Until specific compatibility data are available, it is recommended that MITOXANTRONE-HEXAL not be mixed in the same infusion with other medication.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant. Contraception is advised. Mitoxantrone is considered a potential human teratogen because of its mechanism of action and the developmental effects demonstrated by related medicines. Women 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 medicine. If MITOXANTRONE-HEXAL is used during pregnancy or if the patient becomes pregnant while taking this medicine, the patient should be apprised of the potential risk to the foetus and genetic counselling should be provided.

Lactation

MITOXANTRONE-HEXAL 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-HEXAL, breastfeeding is contraindicated (see section 4.3) and should be discontinued before starting treatment.

Fertility

MITOXANTRONE-HEXAL can be genotoxic. Men who are treated with MITOXANTRONE-HEXAL are therefore advised not to father a child during treatment and for up to 6 months afterwards. In men, no data are available, but tubular atrophy of the testes and reduced sperm counts were observed in animals (see section 5.3). It is advisable to obtain advice about freezing sperm before treatment due to the possibility of irreversible infertility as a result of the treatment with MITOXANTRONE-HEXAL. Women of childbearing potential must be advised to avoid becoming pregnant; should have a negative pregnancy test prior to each dose and use effective contraception during therapy and for at least 4 months after cessation of therapy. Women treated with MITOXANTRONE-HEXAL have an increased risk of transitory or persistent amenorrhoea and therefore preservation of gametes should be considered prior to therapy.

4.7 Effects on ability to drive and use machines

MITOXANTRONE-HEXAL has minor influence on the ability to drive and use machines. Confusion and fatigue may occur following administration of MITOXANTRONE-HEXAL (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most serious side effects with MITOXANTRONE-HEXAL are myocardial toxicity and myelosuppression. The most frequent side effects with MITOXANTRONE-HEXAL are anaemia, leucopenia, neutropenia, infections, amenorrhoea, alopecia, nausea and vomiting.

Infections and infestations

***Frequent*:** Infection (including fatal outcome).

***Less frequent*:** Opportunistic infections, urinary tract infection, upper respiratory tract infection, pneumonia, sepsis.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

***Less frequent*:** Acute myeloid leukaemia, myelodysplastic syndrome, acute leukaemia.

Blood and lymphatic system disorders

Frequent: Myelosuppression, anaemia, neutropenia, leukopenia.

Less frequent: Thrombocytopenia, bone marrow failure, granulocytopenia, haemorrhage/bruising, bleeding, abnormal white blood count.

Immune system disorders

Frequent: Hypersensitivity reactions.

Less frequent: Anaphylaxis/anaphylactoid reactions (including shock), immunosuppression.

Metabolism and nutrition disorders

Frequent: Anorexia

Less frequent: Weight fluctuations, tumour lysis syndrome*, loss of appetite.

* Acute T and B lymphoblastic leukaemia and non-Hodgkin lymphomas (NHL) are most commonly associated with TLS.

Nervous system disorders

***Frequent*:** Non-specific neurological side effects, lethargy.

***Less frequent*:** Anxiety, confusion, drowsiness, paraesthesia, headache.

Eye disorders

Frequent: Scleral discolouration.

Less frequent: Conjunctivitis.

Cardiac disorders

***Frequent*:** Congestive heart failure, myocardial infarction (including fatal events), electrocardiogram abnormal, dysrhythmias, left ventricular ejection fraction decreased.

***Less frequent*:** Arrhythmia, chest pain, cardiomyopathy, sinus bradycardia.

Vascular disorders

Less frequent: Blue discolouration of veins, hypotension, contusion, haemorrhage.

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea.

Gastrointestinal disorders

Frequent: Nausea, vomiting, constipation, diarrhoea, stomatitis.

Less frequent: Mucosal inflammation, abdominal pain, gastrointestinal haemorrhage, taste disturbances.

Hepatobiliary disorders

Frequent: Liver dysfunction.

***Less frequent*:** Hepatotoxicity, elevated aspartate aminotransferase levels.

Skin and subcutaneous tissue disorders

Frequent: Alopecia.

***Less frequent*:** Blue colouring of nails and detachment, rash, skin discolouration, tissue necrosis (after extravasation).

Reproductive system and breast disorders

***Frequent*:** Amenorrhoea, reduction of spermiogenesis.

General disorders and administration site conditions

***Frequent*:** Fatigue, asthenia, pyrexia.

***Less frequent*:** Extravasation*, oedema.

* 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 (see boxed section 4.4). Phlebitis has also been reported at the site of infusion.

Investigations

***Frequent*:** Blue-green discolouration of the urine.

***Less frequent*:** Changes in liver enzymes, serum creatinine, blood urea and bilirubin.

Description of selected adverse reactions

Myocardial toxicity, manifested in its most severe form by potentially irreversible and fatal congestive heart failure (CHF), may occur either during therapy with MITOXANTRONE-HEXAL or months to years after termination of therapy. This risk increases with cumulative dose. In clinical trials cancer patients who received cumulative doses of 140 mg/m^2 either

alone or in combination with other chemotherapeutic agents had a cumulative 2,6 % probability of clinical congestive heart failure.

Myelosuppression is a dose-limiting undesirable effect of MITOXANTRONE-HEXAL. Myelosuppression can be more pronounced and longer lasting in patients who have previously received chemotherapy or radiotherapy. In a clinical trial with acute leukaemia patients, significant myelosuppression occurred in all patients who were given mitoxantrone therapy. Amongst the 80 enrolled patients the median values for the lowest white blood cell count and platelet count were 400/µℓ (WHO grade 4), and 9,500/µℓ (WHO grade 4), respectively. Haematological toxicity is difficult to evaluate in acute leukaemia because traditional parameters of bone marrow depression such as white blood cell and platelet counts are confounded by marrow replacement with leukemic cells.

Tumour lysis syndrome (characterised by hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia) has been observed less frequently during chemotherapy in monotherapy with MITOXANTRONE-HEXAL, as well as during combination chemotherapy.

Paediatric use

Treatment with MITOXANTRONE-HEXAL is not recommended in the paediatric population. Safety and efficacy in paediatric patients have not been established.

4.9 Overdose

In acute or chronic overdose there is an intensification of the observed adverse reactions (see section 4.8). The further course in case of acute and chronic overdose is determined by bone marrow depression in various stages up to agranulocytosis with necrotising angina and critical thrombocytopenia.

There may be ulcerations in the gastrointestinal tract, haemorrhagic enterocolitis with massive bleeding, diarrhoea and persistent signs of kidney and liver toxicity. If an aplasia of the bone marrow due to acute overdose of MITOXANTRONE-HEXAL occurs, it persists longer (about 3 weeks) according to previous experiences. In patients with acute leukaemia, severe stomatitis may occasionally occur. Appropriate measures for prophylaxis and treatment should therefore be taken. In some cases, acute cardiac symptoms in various degrees of severity are possible. Accidental overdoses have been reported. Four patients receiving 140 to 180 mg/m^2 as a single bolus injection died as a result of severe leukopenia with infection.

Treatment

There is no known specific antidote for MITOXANTRONE-HEXAL.

Although patients with severe renal failure have not been studied, MITOXANTRONE-HEXAL is quickly eliminated from the plasma and has a high affinity for tissue. Therefore, it is unlikely that the therapeutic effect or toxicity would be mitigated by peritoneal or haemodialysis.

Haematologic support and antimicrobial therapy may be required during prolonged periods of severe myelosuppression.

After detection of the overdose, a consistent infection prophylaxis with antibiotics has to be initiated. To bypass agranulocytosis and thrombocytopenia, leukocyte and platelet concentrates are suitable.

The management of overdosage is symptomatic and supportive (compensation of fluid and electrolyte balance, monitoring of renal and hepatic function, strict cardiovascular monitoring etc.). Each overdose requires careful monitoring of the clinical findings in order to detect late complications in time (see sections 4.4 and 4.8).

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 26 Cytostatic agents

5.1 Pharmacodynamic properties

Mechanism of action

Mitoxantrone, a DNA-reactive agent that intercalation into deoxyribonucleic acid (DNA) through hydrogen bonding, causes crosslinks and strand breaks. Mitoxantrone also interferes with ribonucleic acid (RNA) and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA. It has a cytocidal effect on proliferating and non-proliferating cultured human cells, suggesting that it may be active against rapidly proliferating and slow-growing neoplasms. Mitoxantrone blocks the cell cycle in G2-phase leading to an increase of cellular RNA and polyploidy.

Mitoxantrone has been shown in vitro to inhibit B cell, T cell, and macrophage proliferation and impair antigen presentation, as well as the secretion of interferon gamma, tumour necrosis factor alpha, and interleukin-2.

Pharmacodynamic effects

Mitoxantrone, a synthetic anthracenedione derivative, is an established cytotoxic, antineoplastic agent. Its therapeutic efficacy has been reported in numerous malignancies.

Clinical efficacy and safety

Treatment with mitoxantrone 12 to 14 mg/m² was effective in the treatment of various cancers. This dose is given in 21 day-cycles, for induction therapy in AML during three consecutive days, for consolidation therapy during two days. Mitoxantrone is active when given alone or in combination with other anticancer agents or corticosteroids.

Mitoxantrone in combination with other cytostatic active substances is effective in the treatment of metastatic breast cancer, also in patients who failed adjuvant therapy with an anthracycline-containing regimen.

Mitoxantrone in combination with corticosteroids improves pain control, and quality of life in patients with advanced castrate resistant prostate cancer, without any improvement in overall survival. Mitoxantrone in combination with cytarabine as initial induction treatment is at least as effective for inducing remission as daunorubicin combinations in adult patients with previously untreated AML. Mitoxantrone alone or in combination with other cytostatic medicinal products shows objective response in patients with several types of NHL. The long-term usefulness of mitoxantrone is limited by emerging cancer resistance which ultimately may result in fatal outcome when used as last-line therapy.

Paediatric population

Safety and efficacy in paediatric patients have not been established.

5.2 Pharmacokinetic properties

Absorption

Mitoxantrone is not absorbed significantly in animals following oral administration.

The pharmacokinetics of mitoxantrone in patients following single-dose intravenous administration can be characterised by a three-compartment model. In patients administered 15 to 90 mg/m^2, there is a linear relationship between dose and the area under the concentration curve (AUC).

Distribution

Distribution to tissue is rapid and extensive. Distribution into testes is negligible. The apparent volume of distribution exceeds 1000 ℓ/m^2. Plasma concentrations decrease rapidly during the

first two hours and slowly thereafter. Mitoxantrone is 78 % bound to plasma proteins. The fraction bound is independent of concentration and is not affected by the presence of phenytoin, doxorubicin, methotrexate, prednisone, prednisolone, heparin or aspirin. Mitoxantrone does not cross the blood-brain barrier.

Biotransformation and elimination

Mitoxantrone is excreted in urine and faeces as either unchanged medicine or as inactive metabolites. In human studies, 10 % and 18 % of the dose was recovered in urine and faeces respectively as either parent substance or metabolite during the 5-day period following medicine administration. Of the material recovered in the urine, 65 % was unchanged mitoxantrone; the remaining 35 % is primarily comprised of two inactive metabolites and their glucuronide conjugates. The metabolites are the mono- and dicarboxylic acid derivatives of mitoxantrone. The pathways leading to the metabolism of mitoxantrone have not been elucidated.

The elimination of mitoxantrone in patients following single-dose intravenous administration can be characterised by a three-compartment model. Elimination of the medicine is slow with a mean half-life of 12 days (range 5 to 18) with a reported elimination phase of between 10 and 40 hours. Several other authors have reported much longer values of between 7 and 12 days. Differences in the estimates may be due to the availability of data at late times after doses, weighting of data and assay sensitivity.

Plasma accumulation of mitoxantrone was not apparent when it was administered either daily for 5 days or as a single dose every 3 weeks.

Special populations

The effect of renal impairment on mitoxantrone pharmacokinetics is unknown. Mitoxantrone clearance is reduced by hepatic impairment. Patients with severe hepatic dysfunction have

an AUC more than three times greater than that of patients with normal hepatic function. Patients with moderately impaired liver function were not observed to have different mitoxantrone clearance compared with patients with normal hepatic function.

There does not seem to be relevant differences in pharmacokinetics of mitoxantrone between elderly and young adult patients.

The effect of gender, race, and renal impairment on mitoxantrone pharmacokinetics is unknown.

Mitoxantrone pharmacokinetics in the paediatric population is unknown.

5.3 Pre-clinical safety data

Single and repeat toxicity studies were conducted in mouse, rat, dog, rabbits, and monkey. The haematopoietic system was the primary target organ of toxicity showing myelosuppression. Heart, kidney, gastrointestinal tract, and testes were additional targets. Tubular atrophy of the testes and decreased sperm counts were observed.

Mitoxantrone was mutagenic and clastogenic in all *in vitro* test systems and in rats *in vivo*. Carcinogenic effects were seen in rat and in male mice.

Treatment of pregnant rats during the organogenesis period of gestation was associated with foetal growth retardation at doses > 0,01 times the recommended human dose on an mg/m^2 basis. When pregnant rabbits were treated during organogenesis, an increased incidence of premature delivery was observed at doses > 0,01 times the recommended human dose on an mg/m^2 basis. No teratogenic effects were observed in these studies, but the maximum doses tested were well below the recommended human dose (0,02 and 0,05 times in rats and rabbits, respectively, on an mg/m^2 basis). No effects were observed on pup development or fertility in the two generation study in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid, hydrochloric acid (for pH adjustment), sodium acetate, sodium chloride, anhydrous sodium sulphate and water for injection.

6.2 Incompatibilities

MITOXANTRONE-HEXAL should not be mixed with the same infusion as heparin since a precipitate may form. Because specific compatibility data are not available, it is recommended that MITOXANTRONE-HEXAL not be mixed in the same infusion with other medicines.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze.

Following admixture, unused portions of MITOXANTRONE-HEXAL should be discarded after 24 hours.

6.5 Nature and contents of container

10 mℓ colourless glass vials (type I) closed with fluoropolymer-coated halobutyl rubber stoppers and sealed with aluminium crimp caps.

6.6 Special precautions for disposal and other handling

Preparation and administration of solution

MITOXANTRONE-HEXAL must never be given subcutaneously, intramuscularly or intra-arterially. There have been reports of local/regional neuropathy, some irreversible, following

intra-arterial injection. Severe local tissue damage may occur if there is extravasation during administration (see section 4.4). MITOXANTRONE-HEXAL must not be given by intrathecal injection.

Severe injury with permanent sequelae can result from intrathecal administration. 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 neurologic sequelae and paralysis with bowel and bladder dysfunction (see section 4.4).

MITOXANTRONE-HEXAL concentrate must be diluted prior to use. The dose of MITOXANTRONE-HEXAL should be diluted to at least 50 mℓ with an appropriate infusion vehicle like 0,9 % sodium chloride or 5 % glucose. MITOXANTRONE-HEXAL may be further diluted with the same solutions and used immediately. MITOXANTRONE-HEXAL should not be mixed with other medicinal products in the same infusion. The diluted solution should be introduced slowly into the tubing as a freely running intravenous infusion with the above solutions - over a period of not less than 3 minutes. The tubing should be attached to a butterfly needle or other suitable device and inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage.

Care should be taken during administration to avoid extravasation at the infusion site and to avoid contact of MITOXANTRONE-HEXAL with the skin, mucous membranes or eyes. Vials should be dispensed in the upright position in order to prevent drops of MITOXANTRONE-HEXAL collecting in the stopper during preparation and leading to potential aerosolisation of the solution. If any signs or symptoms of extravasation have occurred, including burning, pain, pruritus, erythema, swelling, blue discolouration or ulceration, the injection or infusion should be immediately terminated and restarted in another vein above the previous vein or in the contralateral arm. During intravenous administration of MITOXANTRONE-HEXAL, extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If it is known or suspected that

subcutaneous extravasation has occurred, it is recommended that intermittent ice packs be placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and surgery consultation obtained early if there is any sign of a local reaction. The extravasation site should be carefully monitored for signs of necrosis and/or phlebitis that may require further medical attention.

As with other potentially cytotoxic compounds caution in the handling and preparation of MITOXANTRONE-HEXAL solutions must be exercised and the use of protective eye glasses, gloves, mask, overall and other protective clothing is recommended.
A 20 gauge or smaller needle size is recommended as the optimal needle size. Doses should be removed using slightly negative pressure in order to avoid aerosolisation and leakage.
Skin accidentally exposed to MITOXANTRONE-HEXAL should be rinsed copiously with warm water, and if the eyes are involved standard irrigation techniques should be used.
Pregnant staff should be excluded from working with this medicinal product.

Spillage disposal

Spills on equipment and on environmental surfaces may be cleaned using an aqueous solution of calcium hypochlorite (5,5 parts calcium hypochlorite in 13 parts by mass of water for each 1 part by mass of MITOXANTRONE-HEXAL). Wet absorbent tissues in the calcium hypochlorite 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 and dispose of these in a safe manner. Wash the area with water and soak up the water with dry tissues. Appropriate safety equipment such as goggles and gloves should be worn while working with calcium hypochlorite solutions and during the clean-up procedure. All MITOXANTRONE-HEXAL 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 medicinal products.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-lr

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBER

37/26/0168

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 February 2006

10. DATE OF REVISION OF THE TEXT

03 November 2020

Additional countries registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Mitoxantrone-Hexal 20 mg/10 ml	NS2	13/26/0062

ATC Code: A 26 Cytostatic agents

Name and address of manufacturer:

EBEWE Pharma Ges.m.b.H. Nfg.KG
Mondseestraβe 11
A-4866 Unterach
Austria

[1]Company Reg. No.: 1990/001979/07