SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mitoxantrone 2 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for infusion contains 2 mg mitoxantrone (as hydrochloride).
Each vial of 5 ml concentrate for solution for infusion contains 10 mg mitoxantrone (as hydrochloride).
Each vial of 10 ml concentrate for solution for infusion contains 20 mg mitoxantrone (as hydrochloride).
Each vial of 15 ml concentrate for solution for infusion contains 30 mg mitoxantrone (as hydrochloride).

Excipient(s) with known effect:
Each ml of concentrate for solution for infusion contains 3.40mg sodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Appearance: dark blue solution. pH in the range of approximately 3.0 to 4.5 and osmolality in the range of approximately 250 to 300 mOsmol/Kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mitoxantrone 2 mg/ml solution is indicated in the treatment of metastatic breast cancer.
Mitoxantrone 2 mg/ml solution is indicated in the treatment of non-Hodgkin's lymphoma.
Mitoxantrone 2 mg/ml solution is indicated for the treatment of acute myeloid leukaemia (AML) in adults.
Mitoxantrone 2 mg/ml solution in combination regimens is indicated in the remission-induction treatment of blast crisis in chronic myeloid leukaemia.
Mitoxantrone 2 mg/ml solution is indicated in combination with corticosteroids for palliation (e.g. pain relief) related to advanced castrate resistant prostate cancer.

Mitoxantrone 2 mg/ml solution is indicated for treatment of patients with highly active relapsing multiple sclerosis associated with rapidly evolving disability where no alternative therapeutic options exist (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Posology

Mitoxantrone 2 mg/ml solution should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapy agents.

Adults and the elderly:

Metastatic breast cancer, non-Hodgkin's lymphoma:

Monotherapy: The recommended starting dose of mitoxantrone used as a single agent is 14 mg/m^2 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 or less) 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 metastatic breast cancer and non-Hodgkin's lymphoma according to, haematological nadir (which usually occurs about 10 days after dosing).

WBC and platelet nadir		**Time to recovery**	**Subsequent dosing**
If WBC nadir > 1,500/µl and platelet nadir > 50, 000/µl		Recovery ≤ 21 days	Repeat prior dose
If WBC nadir > 1,500/µl and platelet nadir > 50,000/µl		Recovery > 21 days	Withhold until recovery, then repeat the prior dose.
If WBC nadir < 1,500/µl or platelet nadir > 50,000/µl		Any duration	Decrease by 2 mg/m^2 from prior dose after recovery
If WBC nadir < 1,000/µl or platelet nadir > 25,000/µl		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 metastatic 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.

Mitoxantrone has also been used in various combinations for non-Hodgkin's lymphoma; however, data are presently limited and specific regimens cannot be recommended.

In combination regimens Mitoxantrone, in starting doses ranging from 7 to 8 to 10 to 12 mg/m^2, dependent on the combination and frequency used, has shown effectiveness.

As a guide, when mitoxantrone is used in combination chemotherapy with another myelosuppressive agent, the initial dose of mitoxantrone should be reduced by 2 to 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 Therapy in Relapse
The recommended dosage for remission induction is 12 mg/m^2 body surface area administered in a single intravenous dose daily for five consecutive days (total 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
For induction, the recommended dosage is 12 mg/m^2 of mitoxantrone daily on Days 1 to 3 given as an intravenous infusion, and 100 mg/m^2 of cytarabine for 7 days given as a continuous 24-hour infusion on Days 1 to 7.

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 with Mitoxantrone given for 2 days and cytarabine for 5 days, using the same daily dosage levels. If severe or life-threatening non-haematological toxicity is observed during the first induction course, the second induction course should be withheld until toxicity resolves.

Consolidation therapy, which was used in two large randomised multicentre trials, consists of mitoxantrone 12 mg/m^2 given by intravenous infusion daily on Days 1 and 2, and cytarabine, 100 mg/m^2 for 5 days given as a continuous 24-hour infusion on Days 1 to 5. The first course was given approximately 6 weeks after the final induction course; the second was generally administered 4 weeks after the first.

A single course of mitoxantrone 6mg/m^2 intravenous (IV) bolus, etoposide 80 mg/m^2 intravenous for a period of 1 hour, and cytarabine (Ara-C) 1 g/m^2 intravenous for a period of 6 hours daily for 6 days (MEC) showed antileukaemic activity as salvage therapy for refractory AML.

Treatment of blast crisis in chronic myeloid leukaemia
Combination therapy in relapse
The recommended dosage in combination regimens in relapse is 5 to 12 mg/m^2 body surface area given as a single intravenous dose daily over 2-4 consecutive days (maximum dose 48 mg/m^2).

Advanced castrate-resistant prostate cancer
Based on data from two 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, in combination with low oral doses of corticosteroids.

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. 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.

Multiple Sclerosis
The treatment with mitoxantrone should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapeutic agents for the treatment of multiple sclerosis.

This treatment should be used only after assessment of the benefit-risk, particularly concerning the haematological and cardiac risks (see section 4.4).

The treatment must not be initiated in patients who have been previously treated with mitoxantrone.

The recommended dosage of mitoxantrone is usually 12 mg/m^2 body surface area given as a short (approximately 5 to 15 minutes) intravenous infusion that may be repeated every 1-3 months. The maximum lifetime cumulative dose should not exceed 72 mg/m^2 (see section 5.1).
If mitoxantrone is administered repeatedly dosing adjustments should be guided by extent and duration of bone marrow suppression.

Differential blood count within 21 days after mitoxantrone infusion
Signs and symptoms of infection and differential blood count with WHO grade 3: following dose 10 mg/m^2
Signs and symptoms of infection and differential blood count with WHO grade 4: following dose 8 mg/m^2

Differential blood count 7 days before mitoxantrone infusion
Signs and symptoms of infection and differential blood count with WHO grade 1: following dose 9 mg/m^2
Signs and symptoms of infection and differential blood count with WHO grade 2: following dose 6 mg/ m^2
Signs and symptoms of infection and differential blood count with WHO grade 3 to 4: discontinuation of therapy

In case of non-haematological toxicities WHO grade 2 to 3 the following dose should be adjusted to 10 mg/m^2, in case of non-haematological toxicity grade 4 the treatment should be discontinued.

Special populations

Elderly
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 in patients with renal impairment is not established. Mitoxantrone should be used with caution.

Hepatic impairment
The safety of mitoxantrone in patients with hepatic insufficiency is not established. For patients with hepatic impairment dose adjustment may be necessary as mitoxantrone 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 in the paediatric population.

Method of administration
For intravenous use only.
Mitoxantrone concentrate should be slowly injected into a free flowing intravenous infusion of isotonic saline or 5% glucose solution over a period of not less than 3 to 5 minutes. The tubing should be inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage.

Mitoxantrone concentrate also can be administered as a short infusion (15 to 30 minutes) diluted in 50 to 100 ml isotonic saline or 5% glucose solution.

Mitoxantrone concentrate must not be given subcutaneously, intramuscularly, or intra-arterially. Severe local tissue damage may occur if there is extravasation during administration. The medicinal product must also not be given by intrathecal injection.

If any signs or symptoms of extravasation have occurred, including burning, pain, pruritus, erythema, swelling, blue discolouration, or ulceration, the administration should be stopped immediately (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, including sulphites that may be produced during the manufacturing of mitoxantrone.

Mitoxantrone is contraindicated in women who are breast-feeding (see sections 4.4 and 4.6).

Mitoxantrone must not be used in treatment of multiple sclerosis in pregnant women (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Precautions to be taken before handling or administering the medicinal product
Mitoxantrone should be given slowly into a freely flowing intravenous infusion. Mitoxantrone must not 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. To date, only isolated cases of severe local reactions (necroses) have been described due to extravasation. Mitoxantrone 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.

Cardiac function
Myocardial toxicity, manifested in its most severe form by potentially irreversible and fatal congestive heart failure (CHF), may occur either during therapy with mitoxantrone or months to years after termination of therapy. This risk increases with cumulative dose. 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%.

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 medicinal products may increase the risk of cardiac toxicity. 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 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 therapy, and the risk increases with cumulative dose. Cardiac toxicity with mitoxantrone may occur at lower cumulative doses whether or not cardiac risk factors are present.

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

Acute congestive heart failure may occasionally occur in patients treated with mitoxantrone for acute myeloid leukaemia.

This also has been reported for MS patients treated with mitoxantrone. Functional

cardiac changes may occur in patients with multiple sclerosis treated with mitoxantrone. Evaluation of the left-ventricular ejection fraction (LVEF) by echocardiogram or MUGA is recommended prior to administration of the initial dose of mitoxantrone and prior to each dose in multiple sclerosis patients and yearly for up to 5 years after the end of therapy. Cardiotoxicity can occur at any time during mitoxantrone therapy, and the risk increases with cumulative dose. Cardiac toxicity with mitoxantrone may occur at lower cumulative doses whether or not cardiac risk factors are present. Ordinarily, patients with multiple sclerosis should not receive a lifetime cumulative dose greater than 72 mg/m2. Mitoxantrone should not ordinarily be administered to multiple sclerosis patients, with either LVEF of < 50% or a clinically-significant reduction in LVEF.

Bone marrow suppression
Therapy with mitoxantrone should be accompanied by close and frequent monitoring of haematological and chemical laboratory parameters, as well as frequent patient observation. A complete blood count, including platelets, should be obtained prior to administration of the initial dose of mitoxantrone, 10 days following the administration and prior to each subsequent infusion and in the event that signs and symptoms of infection develop. 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.

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 therapy generally should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm3. It is recommended that frequent peripheral blood cell counts are performed on all patients receiving mitoxantrone in order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection.

When mitoxantrone is used in high doses (> 14 mg/m2/d x 3 days) such as indicated for the treatment of leukaemia, severe myelosuppression will occur.

Particular care should be given to assuring full haematological recovery before undertaking consolidation therapy (if this treatment is used) and patients should be monitored closely during this phase. Mitoxantrone administered at any dose can cause myelosuppression.

Secondary acute myeloid leukaemia and myelodysplastic syndrome
Topoisomerase II inhibitors, including mitoxantrone, when used as monotherapy or especially concomitantly with other antineoplastic agents and/or radiotherapy, have been associated with the development of Acute Myeloid Leukaemia or Myelodysplastic Syndrome. Because of the risk of development of secondary malignancies, the benefit-to-risk ratio of mitoxantrone therapy should be determined before starting therapy.

Use after other MS-specific treatments
The safety and efficacy of mitoxantrone have not been studied after treatment with

natalizumab, fingolimod, alemtuzumab, dimethyl fumarate, or teriflunomide.

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 should only be used for metastatic breast cancer.

Infections
Patients who receive immunosuppressive agents like mitoxantrone have a reduced immunological response to infection. Systemic infections should be treated concomitantly with or just prior to commencing therapy with mitoxantrone.

Vaccination
Immunisation with live virus vaccines (e.g. yellow fever vaccination) increases the risk of infection and other adverse reactions such as vaccinia gangrenosa and generalized vaccinia, in patients with reduced immunocompetence, such as during treatment with mitoxantrone. 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 4.5).

Contraception in males and females
Mitoxantrone 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 therapy and for 5 months following completion of treatment. Women of childbearing potential should have a negative pregnancy test prior to each dose, and use effective contraception during therapy and for 8 months following completion of treatment.

Breast-feeding
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, breast-feeding 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 has the potential to be carcinogenic in humans.

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

Discolouration of urine and other tissues

Mitoxantrone may cause a blue-green colouration to the urine for 24 hours after administration, and patients should be advised to expect this during therapy. Bluish discolouration of the sclera, skin and nails may also occur.

Excipient(s) warning:
This medicinal product contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.
Each vial of 5 ml of this medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

Each vial of 10 ml of this medicinal product contains 34.40 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.72% of the recommended maximum daily dietary intake of sodium for an adult.

Each vial of 15 ml of this medicinal product contains 51.00 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2.55% of the recommended maximum daily dietary intake of sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Combining mitoxantrone with potentially cardiotoxic active substances (e.g. anthracyclines) increases the risk of cardiac toxicity.

Topoisomerase II inhibitors, including mitoxantrone, 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) (see section 4.8).

Mitoxantrone causes myelosuppression as an extension of its pharmacological action. Myelosuppresion 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 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 generalized vaccinia, in patients with reduced immunocompetence, such as during treatment with mitoxantrone. 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 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 of mitoxantrone. Inducers of the BCRP transporter could potentially decrease mitoxantrone 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).

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Mitoxantrone 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 therapy and for 5 months following completion of treatment. Women of childbearing potential must be advised to avoid becoming pregnant. They should have a negative pregnancy test prior to each dose and use effective contraception during therapy and for 8 months following completion of treatment.

Pregnancy

There are very limited data on the use of mitoxantrone in pregnant women. Mitoxantrone was not teratogenic in animal studies at doses below human exposure, but caused reproductive toxicity (see section 5.3). Mitoxantrone is considered a potential human teratogen because of its mechanism of action and the developmental effects demonstrated by related agents. For this reason, the use of mitoxantrone to treat MS is contraindicated for pregnant women (see section 4.3). When used for treatment in other indications mitoxantrone should not be administered during pregnancy in particular during the first trimester of pregnancy. In each individual case the benefit of treatment must be weighed up against the possible risk to the foetus. If this medicinal product is used during pregnancy or if the patient becomes pregnant while taking mitoxantrone, the patient should be informed of the potential risk to the foetus and genetic counselling should be provided.

Breast-feeding

Mitoxantrone is excreted in breast-milk and 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, breast-feeding is contraindicated (see section 4.3) and must be discontinued before starting treatment.

Fertility

Women treated with mitoxantrone have an increased risk of transitory or persistent amenorrhoea and therefore preservation of gametes should be considered prior to therapy. For men, no data are available, but tubular atrophy of the testes and reduced sperm counts were observed in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most serious side effects with mitoxantrone are myocardial toxicity and myelosuppression. The most common side effects with mitoxantrone (seen in more than 1 patient in 10) are anaemia, leucopenia, neutropenia, infections, amenorrhoea, alopecia, nausea and vomiting.

Tabulated list of adverse reactions

The table below is based on safety data derived from clinical trials and spontaneous reporting in oncological indications and from clinical trials, post authorisation safety studies and spontaneous reporting for patients treated for multiple sclerosis. Frequencies are defined according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Frequency	**Oncology**	**Multiple Sclerosis**
Infections and Infestations		
Very common	Infection (including fatal outcome)	Infection (including fatal outcome) Urinary tract infection Upper respiratory tract infection
Uncommon	Urinary tract infection Upper respiratory tract infection Sepsis Opportunistic infections	Pneumonia Sepsis Opportunistic infections
Rare	Pneumonia	
Neoplasms benign and malignant (including cysts and polyps)		

Uncommon	Acute myeloid leukaemia, myelodysplastic syndrome, acute leukaemia	Acute myeloid leukaemia, myelodysplastic syndrome, acute leukaemia
Blood and lymphatic system disorders		
Very common	Anaemia Neutropenia Leukopenia	
Common	Thrombocytopenia Granulocytopenia	Anaemia Leukopenia Granulocytopenia White blood cell count abnormal
Uncommon	Myelosuppression Bone marrow failure White blood cell count abnormal	Bone marrow failure Myelosuppression Thrombocytopenia Neutropenia
Immune system disorders		
Uncommon	Anaphylaxis/anaphylactoid reactions (including shock)	Anaphylaxis/anaphylactoid reactions (including shock)
Metabolism and nutrition disorders		
Common	Anorexia	
Uncommon	Weight fluctuations Tumour lysis syndrome*	Anorexia Weight fluctuations
* Acute T and B lymphoblastic leukaemia and non-Hodgkin lymphomas (NHL) are most commonly associated with TLS		
Nervous system disorders		
Common	Lethargy	Headache

Uncommon	Anxiety Confusion Headache Paraesthesia	Anxiety Confusion Paraesthesia Lethargy
Frequency	**Oncology**	**Multiple Sclerosis**
Eye disorders		
Uncommon	Scleral discolouration	Scleral discolouration
Cardiac disorders		
Common	Congestive heart failure Myocardial infarction (including fatal events)	Arrhythmia Electrocardiogram abnormal Left ventricular ejection fraction decreased
Uncommon	Arrhythmia Sinus bradycardia Electrocardiogram abnormal Left ventricular ejection fraction decreased	Congestive heart failure Cardiomyopathy Sinus bradycardia Myocardial infarction (including fatal events)
Rare	Cardiomyopathy	
Vascular disorders		
Uncommon	Contusion Haemorrhage Hypotension	Contusion Haemorrhage Hypotension
Respiratory, thoracic and mediastinal disorders		
Common	Dyspnoea	
Uncommon		Dyspnoea
Gastrointestinal disorders		
Very common	Nausea Vomiting	Nausea
Common	Constipation Diarrhoea Stomatitis	Constipation Diarrhoea Stomatitis Vomiting
Uncommon	Abdominal pain Gastrointestinal haemorrhage Mucosal inflammation Pancreatitis	Abdominal pain Gastrointestinal haemorrhage Mucosal inflammation Pancreatitis
Hepatobiliary disorders		

Common		Elevated aspartate aminotransferase levels
Uncommon	Hepatotoxicity Elevated aspartate aminotransferase levels	Hepatotoxicity
Skin and subcutaneous tissue disorders		
Very common	Alopecia	Alopecia
Uncommon	Erythema Nail disorders Rash Skin discolouration Tissue necrosis (after extravasation)	Nail disorders Rash Skin discolouration Tissue necrosis (after extravasation)
Renal and urinary disorders		
Uncommon	Elevated serum creatinine Elevated blood urea nitrogen levels Nephropathy toxic Urine discolouration	Elevated serum creatinine Elevated blood urea nitrogen levels Nephropathy toxic Urine discolouration
Reproductive system and breast disorders		
Very common		Amenorrhoea*
Uncommon	Amenorrhoea	
* Amenorrhea may be prolonged and may be consistent with premature menopause		
General disorders and administration site conditions		
Common	Asthenia Fatigue Pyrexia	
Uncommon	Oedema Extravasation* Dysgeusia	Asthenia Fatigue Oedema Pyrexia Extravasation* Sudden death**

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

** The casual relationship to mitoxantrone administration is uncertain.

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 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/m2 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. 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.

Multiple sclerosis population

Haematological toxicity
A neutropenia can occur after each administration. This is in general a transient neutropenia with the lowest count of leucocytes at day 10 after the infusion and recovered around day 20. A reversible thrombocytopenia can also be observed. Haematological parameters should be regularly monitored (see section 4.4).

Fatal cases of Acute Myeloid Leukaemia (AML) have been reported (see section 4.4).

Cardiac toxicity
Cases of ECG anomalies have been reported. Cases of congestive heart failure with left-ventricular ejection fraction (LVEF) < 50 % have also been reported (see section 4.4).

Paediatric population
Treatment with mitoxantrone is not recommended in the paediatric population. Safety and efficacy have not been established.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is

important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no known specific antidote for mitoxantrone. 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. Haematological support and antimicrobial therapy may be required during prolonged periods of severe myelosuppression.

Although patients with severe renal failure have not been studied, mitoxantrone is extensively tissue bound and it is unlikely that the therapeutic effect or toxicity would be mitigated by peritoneal or haemodialysis.

Haematopoietic, gastro-intestinal, hepatic or renal toxicity may be seen, depending on the dosage given and the physical condition of the patient.

In cases of overdosage, patients should be monitored closely. Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Anthracyclines and related compounds. ATC code: L01D B07

Mechanism of action
Mitoxantrone, a DNA-reactive agent that intercalates 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 both proliferating and non-proliferating cultured human cells, suggesting lack of cell cycle phase specificity and activity 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. Its presumed mechanism of action in MS is immunosuppression.

Clinical efficacy and safety
Treatment with mitoxantrone 12 to 14 mg/m² was effective in the treatment of various cancers. This dosage 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 cytotoxic 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.

Treatment with mitoxantrone 12 mg/m² administered every three months was superior to 5 mg/m² and placebo in one clinical study with highly active inflammatory active MS disease. A reduction of neurologic disability worsening and frequency of clinical relapses was observed. In the several studies in multiple sclerosis the effective cumulative dose ranged from 36 mg/m2 to 120 mg/m2. Single doses ranged from 5 to 12 mg/m2, dose intervals from once per month to once per 3 months. Also the time course over which the cumulative dose was given ranged from 3 to 24 months. However, cardiotoxicity increases with cumulative doses. A cumulative dose of 72 mg/m² is still effective and associated with less cardiotoxicity than higher cumulative doses. Hence, patients with multiple sclerosis should not receive a lifetime cumulative dose greater than 72 mg/m².

Paediatric population
Safety and efficacy in paediatric patients have not been established.

5.2 Pharmacokinetic properties

Absorption
The pharmacokinetics of mitoxantrone in patients following single-dose intravenous administration can be characterised by a three-compartment model. In patients administered 15-90 mg/m2, there is a linear relationship between dose and the area under the concentration curve (AUC). Plasma accumulation of active substance was not apparent when mitoxantrone was administered either daily for five days or as a single dose every three weeks.

Distribution
Distribution to tissues is extensive: steady-state volume of distribution exceeds 1,000 L/m2. 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. Distribution into testes is relatively low.

Biotransformation and elimination
The pathways leading to the metabolism of mitoxantrone have not been elucidated. Mitoxantrone is excreted slowly in urine and faeces as either unchanged active substance or as inactive metabolites. In human studies, only 10 % and 18 % of the dose were recovered in urine and faeces respectively as either active substance or metabolite during the 5-day period following administration of the medicinal product. Of the material recovered in urine, 65 % was unchanged active substance. The remaining 35 % was composed of monocarboxylic and dicarboxylic acid derivatives and their glucuronide conjugates.

Many of the reported half-life values for the elimination phase are between 10 and 40 hours, but 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, weighing of the data and assay sensitivity.

Special populations
Mitoxantrone clearance may be reduced by hepatic impairment.
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 Preclinical 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/m2 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/m2 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/m2 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

Sodium chloride,

sodium acetate (E 262),

acetic acid (E 260),

water for injections.

6.2 Incompatibilities

The medicinal product must not be mixed with other medicinal products and must only be diluted in the diluents specified under section 6.6 “Special precautions for disposal and other handling”.

6.3 Shelf life

Unopened vial: 18 months.

Chemical and physical stability of the diluted product has been demonstrated for a period of 7 days or 14 days at 15-25°C and 2-8 °C respectively in partially used vials.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Unopened vial and diluted product: Do not store above 25°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

Pack sizes:10 mg/5 ml (vial size 5 ml);

20 mg/10 ml (vial size 15 ml);

30 mg/15 ml (vial size 20 ml).

1, 5, 10 vials

Not all pack sizes may be marketed

Nature of container: glass vials glass type I, 20 mm butyl rubber stoppers.

6.6 Special precautions for disposal

Mitoxantrone 2 mg/ml solution must be diluted in at least 50 ml of one of the following free-flowing intravenous infusions: sodium chloride 0.9% or glucose 5%.

Mitoxantrone must not be mixed with other medicinal products in the same infusion.

After dilution the solution for infusion must be visually inspected prior to use. Only clear solutions practically free from visible particles may be used.

Care must be taken to avoid Mitoxantrone 2 mg/ml solution coming into contact with the skin, the mucous membranes or the eyes. It is recommended that glasses, gloves and protective clothing be worn during preparation and administration. Mitoxantrone 2 mg/ml solution may cause staining. If the skin accidentally comes into contact with Mitoxantrone 2 mg/ml solution, it should be rinsed with copious amounts of warm water. The standard irrigation techniques apply for the eyes.

The following cleaning procedure is recommended if mitoxantrone is spilled on equipment or surrounding surfaces. Prepare a 50% solution of fresh concentrated bleach *(about 10-13% available chlorine)* (any suitable recognised 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 completely disappeared. Mop up the tissues with dry tissues. Wash the area with water and soak up the water with dry tissues. Appropriate protective clothing should be worn during the cleaning procedure. All items contaminated with mitoxantrone (e.g. syringes, needles, tissues, etc.) must be treated as toxic waste and the appropriate guidelines must be followed. Incineration is recommended. The statement about safety equipment must be complied with.

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

7 MARKETING AUTHORISATION HOLDER

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