SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ONKOTRONE® INJECTION
2 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 2 mg mitoxantrone (as hydrochloride).

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Sterile dark blue aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Onkotrone Injection is indicated for the treatment of:

- Metastatic breast cancer
- Non-Hodgkin's Lymphoma
- Acute myeloid leukaemia (AML) in adults
- In combination regimens is indicated in the remission-induction treatment of blast crisis in chronic myeloid leukaemia
- In combination with corticosteroids for palliation (e.g. pain relief) related to advanced castrate resistant prostate cancer.

4.2 Posology and method of administration

Posology

Onkotrone should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapy agents.

Metastatic breast cancer, non-Hodgkin’s lymphoma

Single agent therapy
The recommended initial dosage of mitoxantrone used as a single agent is 14 mg/m^2 of body surface area, given as a single intravenous dose, which may be repeated at 21-day intervals. A lower initial dosage (12 mg/m^2 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 judgment 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 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 of body surface area, given as a single intravenous dose daily for five consecutive days (total of 60 mg/m^2). In clinical studies with a dosage of 12 mg/m^2 daily for 5 days,

patients who achieved a complete remission did so as a result of the first induction course.

Combination Therapy
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/m2 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 6 mg/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
Single dose therapy in relapse
The recommended dosage in relapse is 10 to 12 mg/m^2 body surface area given as a single intravenous dose daily over 5 consecutive days (total of 50 to 60 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.

<u>Special populations</u>
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
Onkotrone concentrate should be given by intravenous infusion only. Onkotrone 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.
Onkotrone 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.
Onkotrone 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).

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.

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/mm^3. 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/m^2/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.

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 generalised 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 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 9 months after cessation of therapy.

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.

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 generalised 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 and at least 6 months after therapy. 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 9 months after cessation of therapy.

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. 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 Onkotrone Injection have an increased risk of transitory or persistent amenorrhoea and therefore preservation of gametes should be considered prior to therapy. In 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. 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	**Adverse Reaction**
Infections and Infestations	
Very common	Infection (including fatal outcome)
Uncommon	Urinary tract infection Upper respiratory tract infection Sepsis Opportunistic infections
Rare	Pneumonia
Neoplasms benign and malignant (including cysts and polyps)	
Uncommon	Acute myeloid leukaemia, myelodysplastic syndrome, acute leukaemia
Blood and lymphatic system disorders	
Very common	Anaemia Neutropenia Leukopenia
Common	Thrombocytopenia Granulocytopenia
Uncommon	Myelosuppression Bone marrow failure White blood cell count abnormal
Immune system disorders	
Uncommon	Anaphylaxis/anaphylactoid reactions (including shock)
Metabolism and nutrition disorders	
Common	Anorexia
Uncommon	Weight fluctuations Tumour lysis syndrome*
* Acute T and B lymphoblastic leukaemia and non-Hodgkin lymphomas (NHL) are most commonly associated with TLS	

Nervous system disorders	
Common	Lethargy
Uncommon	Anxiety Confusion Headache Paraesthesia
Eye disorders	
Uncommon	Scleral discolouration
Cardiac disorders	
Common	Congestive heart failure Myocardial infarction (including fatal events)
Uncommon	Arrhythmia Sinus bradycardia Electrocardiogram abnormal Left ventricular ejection fraction decreased
Rare	Cardiomyopathy
Vascular disorders	
Uncommon	Contusion Haemorrhage Hypotension
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea
Gastrointestinal disorders	
Very common	Nausea Vomiting
Common	Constipation Diarrhoea Stomatitis
Uncommon	Abdominal pain Gastrointestinal haemorrhage Mucosal inflammation Pancreatitis
Hepatobiliary disorders	
Uncommon	Hepatotoxicity Elevated aspartate aminotransferase levels
Skin and subcutaneous tissue disorders	
Very common	Alopecia
Uncommon	Erythema 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
Reproductive system and breast disorders	
Uncommon	Amenorrhoea
General disorders and administration site conditions	
Common	Asthenia Fatigue Pyrexia
Uncommon	Oedema Extravasation* Dysgeusia
* 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.	

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/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. 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.

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 Yellow Card Scheme at: 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, gastrointestinal, hepatic or renal toxicity may be seen, depending on the dosage given and the physical condition of the patient. In cases of overdosage patients should be monitored closely. Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Anthracyclines and related substances
ATC-Code: L01DB07

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.

Clinical efficacy and safety
Treatment with mitoxantrone 12 to 14 mg/m^2 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 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
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/m^2, 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/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. 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/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

Sodium chloride
Sodium acetate

Acetic acid
Water for Injections
Carbon dioxide
Nitrogen

6.2 Incompatibilities

Onkotrone Injection solution must not be mixed together with other drugs in an infusion solution.

Heparin must not be added to Onkotrone Injection solutions as precipitation may occur.

6.3 Shelf Life

3 years unopened
8 hours after dilution

6.4 Special Precautions for Storage

Do not store above 25°C
Do not freeze

6.5 Nature and Contents of Container

Containers:
Clear glass type 1 injection vial with rubber stopper and aluminium flange cap.

Contents:
Onkotrone Injection is a sterile dark blue aqueous solution of mitoxantrone hydrochloride equivalent to 2 mg/ml. It is available in the following vial sizes:

1 injection vial containing 20 mg mitoxantrone in 10 ml injection solution
1 injection vial containing 25 mg mitoxantrone in 12.5 ml injection solution
1 injection vial containing 30 mg mitoxantrone in 15 ml injection solution

6.6 Instruction for Use/Handling

Onkotrone Injection should only be handled by adequately trained personnel. Pregnant and lactating staff should not be involved in the dilution or administration of Onkotrone Injection.

Care should be taken when handling Onkotrone Injection to avoid contact with the skin, mucous membranes and eyes. The use of protective gloves, gown and safety goggles is recommended during preparation, administration and disposal. Work surfaces should be covered with disposable plastic backed absorbent paper. Aerosol generation should be minimised. Onkotrone injection can cause staining. If contact of Onkotrone Injection with the skin or mucous membranes does occur, the contact area should be immediately copiously washed with warm water. Eyes must be thoroughly rinsed with water and if necessary, an ophthalmologist should be consulted.

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

The manufacturing process may cause a slight over-pressure in the injection vial. Caution should therefore be exercised when piercing the injection vial.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 00116/0398

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/07/2009

10 DATE OF REVISION OF THE TEXT

16/06/2025