

Annex III

Summary of product characteristics, labelling and package leaflet

Note:

This Summary of Product Characteristics, labelling and package leaflet is the outcome of the referral procedure to which this Commission decision relates.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Novantrone and associated names (see Annex I) 2 mg/ml concentrate for solution for infusion
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect:

For the full list of excipients, see section 6.1.
[To be completed nationally]

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mitoxantrone is indicated in the treatment of metastatic breast cancer.

Mitoxantrone is indicated in the treatment of non-Hodgkin's lymphoma.

Mitoxantrone is indicated for the treatment of acute myeloid leukaemia (AML) in adults.

Mitoxantrone in combination regimens is indicated in the remission-induction treatment of blast crisis in chronic myeloid leukaemia.

Mitoxantrone is indicated in combination with corticosteroids for palliation (e.g. pain relief) related to advanced castrate resistant prostate cancer.

Mitoxantrone 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 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/m² of body surface area, given as a single intravenous dose, which may be repeated at 21-day intervals. A lower initial dosage

(12 mg/m² 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/m², 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/m² 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/m² of body surface area, given as a single intravenous dose daily for five consecutive days (total of 60 mg/m²). In clinical studies with a dosage of 12 mg/m² daily for 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/m² of mitoxantrone daily on Days 1 to 3 given as an intravenous infusion, and 100 mg/m² 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/m² 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/m² intravenous (IV) bolus, etoposide 80 mg/m² intravenous for a period of 1 hour, and cytarabine (Ara-C) 1 g/m² 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/m² body surface area given as a single intravenous dose daily over 5 consecutive days (total of 50 to 60 mg/m²).

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/m² 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/m² 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/m² 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/m² (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/m²

Signs and symptoms of infection and differential blood count with WHO grade 4: following dose 8 mg/m²

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/m²

Signs and symptoms of infection and differential blood count with WHO grade 2: following dose 6 mg/m²

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/m², 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

Novantrone concentrate should be given by intravenous infusion only.

Novantrone 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.

Novantrone 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.

Novantrone 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/m² 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 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.

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. 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 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 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 4 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. 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. 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 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Frequency	Oncology	Multiple Sclerosis
<i>Infections and Infestations</i>		
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	
<i>Neoplasms benign and malignant (including cysts and polyps)</i>		
Uncommon	Acute myeloid leukaemia, myelodysplastic syndrome, acute leukaemia	Acute myeloid leukaemia, myelodysplastic syndrome, acute leukaemia
<i>Blood and lymphatic system disorders</i>		
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	Bone marrow failure Myelosuppression

Frequency	Oncology	Multiple Sclerosis
	abnormal	Thrombocytopenia Neutropenia
<i>Immune system disorders</i>		
Uncommon	Anaphylaxis/anaphylactoid reactions (including shock)	Anaphylaxis/anaphylactoid reactions (including shock)
<i>Metabolism and nutrition disorders</i>		
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		
<i>Nervous system disorders</i>		
Common	Lethargy	Headache
Uncommon	Anxiety Confusion Headache Paraesthesia	Anxiety Confusion Paraesthesia Lethargy
<i>Eye disorders</i>		
Uncommon	Scleral discolouration	Scleral discolouration
<i>Cardiac disorders</i>		
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	
<i>Vascular disorders</i>		
Uncommon	Contusion Haemorrhage Hypotension	Contusion Haemorrhage Hypotension
<i>Respiratory, thoracic and mediastinal disorders</i>		
Common	Dyspnoea	
Uncommon		Dyspnoea

Frequency	Oncology	Multiple Sclerosis
<i>Gastrointestinal disorders</i>		
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
<i>Hepatobiliary disorders</i>		
Common		Elevated aspartate aminotransferase levels
Uncommon	Hepatotoxicity Elevated aspartate aminotransferase levels	Hepatotoxicity
<i>Skin and subcutaneous tissue disorders</i>		
Very common	Alopecia	Alopecia
Uncommon	Erythema Nail disorders Rash Skin discolouration Tissue necrosis (after extravasation)	Nail disorders Rash Skin discolouration Tissue necrosis (after extravasation)
<i>Renal and urinary disorders</i>		
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
<i>Reproductive system and breast disorders</i>		
Very common		Amenorrhoea*
Uncommon	Amenorrhoea	
* Amenorrhoea may be prolonged and may be consistent with premature menopause		
<i>General disorders and administration site conditions</i>		
Common	Asthenia	

Frequency	Oncology	Multiple Sclerosis
	Fatigue Pyrexia	
Uncommon	Oedema Extravasation* Dysgeusia	Asthenia Fatigue Oedema Pyrexia Extravasation* Sudden death**
<p>* 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.</p> <p>** The casual relationship to mitoxantrone administration is uncertain.</p>		

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/ μ l (WHO grade 4), and 9.500/ μ l (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 listed in [Appendix V](#)**.

4.9 Overdose

There is no known specific antidote for mitoxantrone. Accidental overdoses have been reported. Four patients receiving 140 to 180 mg/m² 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 cytotoxic 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 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.

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

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

Not all pack sizes may be marketed.

[To be completed nationally]

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}

{tel}

{fax}

{e-mail}

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

{DD/MM/YYYY}

{DD month YYYY}

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Novantrone and associated names (see Annex I) 2 mg/ml concentrate for solution for infusion
[See Annex I - To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Mitoxantrone
[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.
[To be completed nationally]

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.
[To be completed nationally]

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[To be completed nationally]

8. EXPIRY DATE

[To be completed nationally]

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

{tel}

{fax}

{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

[To be completed nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

17. UNIQUE IDENTIFIER – 2D BARCODE

<Not applicable>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<Not applicable>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Novantrone and associated names (see Annex I) 2 mg/ml concentrate for solution for infusion
[See Annex I - To be completed nationally]
Mitoxantrone
Intravenous use

2. METHOD OF ADMINISTRATION

[To be completed nationally]

3. EXPIRY DATE

[To be completed nationally]

4. BATCH NUMBER

[To be completed nationally]

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

[To be completed nationally]

PACKAGE LEAFLET

Package leaflet: Information for the patient

Novantrone and associated names (see Annex I) 2 mg/ml concentrate for solution for infusion

[See Annex I - To be completed nationally]

Mitoxantrone

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Novantrone is and what it is used for
2. What you need to know before you use Novantrone
3. How to use Novantrone
4. Possible side effects
5. How to store Novantrone
6. Contents of the pack and other information

1. What Novantrone is and what it is used for

Novantrone contains the active substance mitoxantrone. Novantrone belongs to the group of medicines known as antineoplastic or anti-cancer medicines. It also belongs to the subgroup of anti-cancer medicines called anthracyclines. Novantrone prevents cancer cells from growing, as a result of which they eventually die. The medicine also suppresses the immune system and is used because of this effect to treat a specific form of multiple sclerosis when there are no alternative treatment options.

Novantrone is used in the treatment of:

- advanced stage (metastatic form) of breast cancer;
- a form of lymph node cancer (non-Hodgkin's lymphoma);
- a cancer of the blood in which the bone marrow (the spongy tissue inside the large bones) makes too many white blood cells (acute myeloid leukaemia);
- a cancer of the white blood cells (chronic myeloid leukaemia) at a stage where it is difficult to control the number of white blood cells (blast crisis). Novantrone is used in combination with other medicinal products in this indication;
- pain caused by prostate cancer at an advanced stage of prostate cancer in combination with corticosteroids;
- highly active relapsing multiple sclerosis associated with rapidly evolving disability where no alternative therapeutic options exist (see sections 2 and 3).

2. What you need to know before you use Novantrone

Do not use Novantrone:

- if you are allergic to mitoxantrone or any of the other ingredients of this medicine (see section 6);
- if you are allergic to sulphite;
- if you have a form of asthma (bronchial asthma) with sulphite allergy;
- if you are breast-feeding (see section "pregnancy and breast-feeding").

For use as treatment of multiple sclerosis:

- if you are pregnant.

Warnings and precautions

Novantrone should be administered under the supervision of a doctor experienced in the use of cancer medicines that are toxic to your cells (cytotoxic chemotherapy agents).

Novantrone should be given by slow and freely flowing infusion into the vein.

Novantrone must not be administered under the skin (subcutaneous), in a muscle (intramuscular), or into the artery (intra-arterial). Severe local tissue damage may occur if Novantrone leaks in surrounding tissue (extravasation) during administration.

Novantrone must also not be injected into the space under the brain or spinal cord (intrathecal injection) as this can result in severe injury with permanent impairment.

Talk to your doctor or, pharmacist or nurse before using Novantrone:

- if you have liver problems;
- if you have kidney problems;
- if you have used Novantrone before;
- if your heart is not working well;
- if you had prior radiotherapy of the chest;
- if you already use other medicines that affect your heart;
- if you had previous therapies with anthracyclines or anthracenediones, such as daunorubicin or doxorubicin;
- if your bone marrow is not working well (is depressed) or if you are in generally poor health;
- if you have an infection. This infection should be treated before taking Novantrone;
- if you plan a vaccination or immunisation during treatment. Vaccinations and immunisations may not work during treatment with Novantrone and for 3 months after the end of treatment;
- if you are pregnant or if you and your partner are trying to become pregnant;
- if you are breast-feeding. You should stop breast-feeding before taking Novantrone.

Tell your doctor or pharmacist or nurse immediately if you get any of the following signs or symptoms during treatment with Novantrone:

- fever, infections, unexplained bleeding or bruising, weakness and easy fatigability;
- breathlessness (including breathlessness at night), cough, fluid retention (swelling) in the ankles or legs, heart fluttering (irregular heart beat). This may occur either during or months to years after therapy with Novantrone.

Your doctor may need to adjust your treatment or stop Novantrone temporarily or permanently.

Blood tests prior and during treatment with Novantrone

Novantrone may affect your blood cell counts. Before you start Novantrone and during treatment, your doctor will do a blood test to count the number of your blood cells. Your doctor will carry out blood tests more often, in which he will in particular monitor the number of white blood cells (neutrophilic leucocytes) in the blood:

- if you have a low count of a specific type of white blood cells (neutrophils) (less than 1,500 cells/mm³);
- if you use Novantrone in high doses (>14 mg/m² per day x 3 days).

Heart function tests prior and during treatment with Novantrone

Novantrone may damage your heart and cause a deterioration of your heart function or in more severe cases heart failure. You are more prone to these side effects if you take higher doses of Novantrone or:

- if your heart is not working well;

- if you had prior treatment of the chest with radiation;
- if you already use other medicines that affect your heart;
- if you had previous therapies with anthracyclines or anthracenediones, such as daunorubicin or doxorubicin.

Your doctor will do heart function tests before you start Novantrone and at regular intervals during therapy. If you receive Novantrone to treat multiple sclerosis your doctor will test your heart function before the start of therapy, prior to each subsequent dose and yearly for up to 5 years after the end of therapy.

Acute myeloid leukemia (AML) and Myelodysplastic syndrome

A group of anticancer medicines (topoisomerase II inhibitors), including Novantrone, may cause the following diseases when used alone but especially in combination with other chemotherapy and/or radiotherapy:

- cancer of white blood cells (acute myeloid leukaemia, AML)
- a bone marrow disorder that causes abnormally shaped blood cells and leads to leukaemia (myelodysplastic syndrome)

Discolouration of urine and other tissues

Mitoxantrone may cause a blue-green colouration to the urine for 24 hours after administration. A bluish discolouration of the whites of your eyes, skin and nails may also occur.

Contraception in men and women

Men must not father a child and should 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. If this medicine is used during pregnancy or if you become pregnant while taking this medicine, inform your doctor as there may be risks to the foetus.

Fertility

This medicine might increase the risk for transitory or persistent absence of menstruation (amenorrhoea) in women of childbearing age.

Children and adolescents

There is little experience in children and adolescents.

Do not give this medicine to children and adolescents from birth up to age of 18 years as safety and efficacy in children and adolescents have not been established.

Other medicines and Novantrone

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. It is particularly important that you mention any of the following medicines.

Medicines which may increase the risk of side effects with Novantrone:

- Medicines that can damage your heart (e.g. anthracyclines).
- Medicines that suppress the bone marrow's production of blood cells and platelets (myelosuppressive agents).
- Medicines that suppress your immune system (immunosuppressive agents).
- Antivitamin K, in particular if you are taking Novantrone because you have cancer.
- Topoisomerase II inhibitors (a groups of anticancer medicines including mitoxantrone) in combination with other chemotherapy and/or radiotherapy. These can cause:
 - o cancer of white blood cells (acute myeloid leukaemia, AML);
 - o a bone marrow disorder that causes abnormally shaped blood cells and leads to leukaemia (myelodysplastic syndrome).

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

These medicines should be used with care or may need to be avoided during your treatment with Novantrone. If you are taking any of these, your doctor might need to prescribe an alternative medicine for you.

You should also tell your doctor if you are already taking Novantrone and you are prescribed a new medicine that you have not already taken at the same time as Novantrone.

Vaccinations and immunisation (protection against the vaccination substances) may not work during treatment with Novantrone and for three months after the end of treatment.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.

Pregnancy

Novantrone may cause damage to your unborn child. Therefore you should avoid becoming pregnant. Novantrone must not be used during pregnancy for treatment of multiple sclerosis (specifically in the first three months of the pregnancy).

If you become pregnant during the treatment with Novantrone, you must tell your doctor immediately and stop treatment with Novantrone.

You should avoid becoming pregnant. Men must use an effective method of contraception during the treatment and for at least 6 months after discontinuing the treatment. Women of child-bearing potential should have a negative pregnancy test prior to each dose and must practise effective contraception for at least 4 months after stopping the treatment with Novantrone.

Breast-feeding

Novantrone is secreted into breast milk and may cause serious adverse reactions in your baby. You must not breast-feed while using mitoxantrone and for up to one month after the last administration.

Fertility

Novantrone might increase the risk for transient or persistent absence of menstruation (amenorrhoea) in women of childbearing age. Therefore you should talk to your doctor if you are planning to become pregnant in the future; your eggs may need to be frozen. In men, no data are available. However, in male animals, damage to the testes and decreased sperm counts were observed.

Driving and using machines

Novantrone has a minor effect on your ability to drive and use machines. This is caused by possible side effects, such as confusion or feeling tired (see section 4).

If you suffer from these side effects, do not drive any vehicles and/or use any machines.

3. How to use Novantrone

Posology and method of administration

Novantrone will be given to you under supervision of a doctor experienced in the use of cytotoxic chemotherapy agents. It must always be administered as an intravenous infusion (in a vein) and must always be diluted before. The infusion liquid can leak out of the vein into the tissue (extravasation). If this happens, the infusion must be stopped and restarted in another vein. You should avoid contact with Novantrone, especially with the skin, mucous membranes (moist body surfaces, such as the lining of the mouth) and eyes. The individual dose of Novantrone is calculated by your doctor. The recommended dose is based on your body surface area, which is calculated in square metres (m²) using your height and

weight. In addition your blood will be tested regularly during the treatment. The dosage of the medicine will be adjusted in accordance with the results of these tests.

The usual dose is:

Metastatic breast cancer, non-Hodgkin's lymphoma

If Novantrone is used alone:

The recommended initial dosage of Novantrone is 14 mg/m² of body surface area, given as a single intravenous dose, which may be repeated at 21-day intervals, if your blood values have returned to acceptable levels.

A lower initial dosage (12 mg/m² or less) is recommended in patients with low bone marrow reserves e.g. due to prior chemotherapy or poor general condition.

Your doctor will decide precisely which subsequent dosage you need.

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.

Combination therapy (if used with other agents)

Novantrone has been given as part of combination therapy. In metastatic breast cancer, combinations of Novantrone with other cytotoxic agents including cyclophosphamide and 5-fluorouracil or methotrexate and mitomycin C have been shown to be effective.

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

As a guide, when Novantrone is used in combination chemotherapy, the initial dose of Novantrone should be reduced by 2-4 mg/m² below the doses recommended when Novantrone is used alone.

Acute myeloid leukaemia:

If used alone for recurrence (return of the cancer)

The recommended dosage for remission induction is 12 mg/m² of body surface area, given as a single intravenous dose daily for five consecutive days (total of 60 mg/m² per 5 days).

If used with other agents against cancer:

Your doctor will decide exactly what dosage you need. This dose might be adjusted if:

- The combination of medicines reduces the production of white and red blood cells as well as platelets in your bone marrow more than Novantrone used alone;
- If you have serious liver or kidney problems.

Treatment of blast crisis in (chronic) myeloid leukaemia

Used alone for recurrence

The recommended dosage in relapse is 10 to 12 mg/m² body surface area given as a single intravenous dose daily over 5 consecutive days (total of 50 to 60 mg/m²).

Advanced castrate-resistant prostate cancer

The recommended dosage of Novantrone is 12 to 14 mg/m² given as a short intravenous infusion every 21 days, in combination with low oral doses of corticosteroids (hormonal medicines that suppress the immune system).

Multiple Sclerosis

Novantrone will be given to you under the supervision of a doctor experienced in the use of cytotoxic chemotherapeutic agents for the treatment of multiple sclerosis.

The recommended dosage of mitoxantrone is usually 12 mg/m² body surface area given as a short (approximately 5 to 15 minutes) intravenous infusion that may be repeated every 1 to 3 months. The maximum lifetime cumulative dose should not exceed 72 mg/m².

If mitoxantrone is administered repeatedly, dosing adjustments should be guided by extent and duration of the reduction in the number of white and red blood cells as well as platelets in your blood.

Elderly patients

Elderly patient should receive doses at the low end of the dosing range due to possible reduced liver, kidney or heart function and of possible illness or treatment with other medicines.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most serious side effects are damage to the heart (myocardial toxicity) and myelosuppression (reduced activity of the bone marrow).

Some side effects could be serious

If any of the following happen, tell the doctor immediately:

- If your skin becomes pale and you feel weak or experience sudden shortness of breath, this can be sign of a reduction in red blood cells.
- Unusual bruising or bleeding, such as coughing up blood, blood in your vomit or urine, or black stools (potential sign of platelet reduction).
- New or worsening breathing difficulties.
- Chest pain, breathlessness, changes in your heartbeat (fast or slow), fluid retention (swelling) in the ankles or legs (potential signs or symptoms of heart problems).
- Severe itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), or if you feel you like you are going to faint, these may be signs of severe allergic reaction.
- Fever or infections.

For patients being treated for cancer:

Very Common (may affect more than 1 in 10 people)

- Infections.
- Low number of red blood cells which can cause a feeling of tiredness and shortness of breath (anaemia). You may require a blood transfusion.
- Low number of special white blood cells (neutrophils and leukocytes)
- Nausea (feeling sick).
- Vomiting (being sick).
- Hair loss.

Common (may affect up to 1 in 10 people)

- Low level of platelets – which may cause bleeding or bruising.
- Low number of special white blood cells (granulocytes).
- Loss of appetite.
- Tiredness, weakness and lack of energy.
- Congestive heart failure (severe condition where the heart cannot anymore pump enough blood).
- Heart attack.
- Shortness of breath.
- Constipation.

- Diarrhoea.
- Inflammation of the mouth and lips.
- Fever.

Uncommon (may affect up to 1 in 100 people)

- Reduced activity of the bone marrow. Your bone marrow can be more depressed or be depressed for a longer period if you have had chemotherapy or radiotherapy.
- Insufficient production of blood cells in the bone marrow (bone marrow failure).
- Abnormal number of white blood cells.
- Severe allergic reaction (anaphylactic reaction including anaphylactic shock) – you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing, and you may feel you are going to faint).
- Infections of the upper airways.
- Infections of the urinary tract.
- Blood poisoning (sepsis).
- Infections caused by microorganisms which do not normally cause diseases with a healthy immune system (opportunistic infections).
- Cancer of the white blood cells (acute myeloid leukemia (AML)).
- Bone marrow abnormality which causes the formation of abnormal blood cells which leads to leukaemia (myelodysplastic syndrome (MDS)).
- Changes in weight.
- Metabolic disturbances (tumour lysis syndrome).
- Anxiety.
- Confusion.
- Headache.
- Tingling sensation.
- Irregular heart beat or slowed heart beat.
- Abnormal electrocardiogram.
- Reduction of the volume of blood that the left ventricle can pump, with no symptoms.
- Bruising.
- Heavy bleeding.
- Low blood pressure.
- Abdominal pain.
- Bleeding in your stomach or bowels, this may include blood in vomit, bleeding when emptying the bowels or black tarry stool.
- Mucosal inflammation.
- Inflammation of the pancreas.
- Liver abnormalities.
- Skin inflammations (erythema).
- Nail abnormalities (e.g. detachment of the nail from the nail bed, changes in nail texture and structure).
- Rash.
- Changes to the colour of the whites of the eyes.
- Skin discolouration.
- Leakage of fluid into surrounding tissue (extravasation):
 - o Reddening (erythema).
 - o Swelling.
 - o Pain.
 - o Burning feeling and/or discolouration of the skin.
 - o Death of tissue cells which can lead to the need to remove dead cells and skin transplantation.
- Abnormal results of blood tests to check liver and kidney functions (raised aspartate aminotransferase levels, elevated creatinine and urea nitrogen concentration in the blood).
- Damage to the kidneys, causing swelling and weakness (nephropathy).

- Urine discolouration.
- Abnormal absence of menstruation (amenorrhoea).
- Swelling (oedema).
- Taste disturbances.

Rare (may affect up to 1 in 1,000 people)

- Lung inflammation (pneumonia).
- Damages to the heart muscle preventing it from pumping properly (cardiomyopathy).

For patients being treated for Multiple Sclerosis:

Very Common (may affect more than 1 in 10 people)

- Infections, including infections of the upper airways and urinary tract.
- Nausea (feeling sick).
- Hair loss.
- Abnormal absence of menstruation (amenorrhea).

Common (may affect up to 1 in 10 people)

- Low number of red blood cells which can cause a feeling of tiredness and shortness of breath (anaemia). You may require a blood transfusion.
- Low number of special white blood cells (granulocytes and leukocytes).
- Constipation.
- Vomiting (being sick).
- Diarrhoea.
- Inflammation of the mouth and lips.
- Abnormal number of white blood cells.
- Headache.
- Irregular heart beat.
- Abnormal electrocardiogram.
- Reduction of the volume of blood that the left ventricle can pump, with no symptoms.
- Abnormal results of blood tests to check liver function (raised aspartate aminotransferase levels).

Uncommon (may affect up to 1 in 100 people)

- Lung inflammation (pneumonia).
- Blood poisoning (sepsis).
- Infections caused by microorganisms which do not normally cause diseases with a healthy immune system (opportunistic infections).
- Cancer of the white blood cells (acute myeloid leukemia (AML)).
- A bone marrow abnormality which causes the formation of abnormal blood cells which leads to leukaemia (myelodysplastic syndrome (MDS)).
- Insufficient production of blood cells in the bone marrow (bone marrow failure).
- Reduced activity of the bone marrow. Your bone marrow can be more depressed or be depressed for a longer period if you have had chemotherapy or radiotherapy.
- Low level of platelets – which may cause bleeding or bruising.
- Low number of special white blood cells (neutrophils).
- Severe allergic reaction (anaphylactic reaction including anaphylactic shock) – you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing, and you may feel you are going to faint).
- Loss of appetite.
- Changes in weight.
- Anxiety.
- Confusion.

- Tingling sensation.
- Tiredness, feeling weak and having no energy.
- Severe condition where the heart cannot anymore pump enough blood (congestive heart failure).
- Damages to the heart muscle preventing it from pumping properly (cardiomyopathy).
- Slowed heart beat.
- Heart attack.
- Unusal bruising.
- Heavy bleeding.
- Low blood pressure.
- Shortness of breath.
- Abdominal pain.
- Bleeding in your stomach or bowels, this may include blood in vomit, bleeding when emptying the bowels or black tarry stool.
- Mucosal inflammation.
- Inflammation of the pancreas.
- Liver abnormalities.
- Nail abnormalities (e.g. detachment of the nail fro the nail bed, changes in nail texture and structure).
- Rash.
- Changes to the colour of the whites of the eyes.
- Skin discolouration.
- Leakage of fluid into surrounding tissue (extravasation):
 - o Reddening (erythema).
 - o Swelling.
 - o Pain.
 - o Burning feeling and/or discolouration of the skin.
 - o Death of tissue cells which can lead to the need to remove dead cells and skin transplantation.
- Abnormal results of blood tests to check liver and kidney functions (elevated creatinine and urea nitrogen concentration in the blood).
- Damage to the kidneys, causing swelling and weakness (nephropathy).
- Urine discolouration.
- Swelling (oedema).
- Fever.
- Sudden death.

Rare (may affect up to 1 in 1,000 people)

None.

Reporting of side effects

If you get any side effects, talk to your doctor or, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Novantrone

[To be completed nationally]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

6. Contents of the pack and other information

What Novantrone contains

[To be completed nationally]

What Novantrone looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}

{tel}

{fax}

{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last revised in {month YYYY}.

[To be completed nationally]

Other sources of information

Detailed information on this medicine is available on the website of {MS/Agency}