# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

ONKOTRONE Concentrate
2 mg/ml concentrate for solution for infusion.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

## 3 PHARMACEUTICAL FORM

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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Onkotrone Concentrate is indicated for the treatment of:

- Advanced breast cancer
- Non-Hodgkin's Lymphoma
- Adult acute non-lymphocytic leukaemia
- Non-resectable primary hepatocellular carcinoma

### 4.2 Posology and method of adminstration

*Intravenous application:*

**1. Advanced Breast Cancer, Non-Hodgkin's Lymphoma, Hepatocellular Carcinoma**

During monotherapy, a dose of mitoxantrone 14 mg/m$^2$ is recommended as the initial dose for the first cycle. This dose can be repeated after 21 days.

In patients with diminished bone marrow reserves as a result of previous radiation and/or chemotherapy or those in a general poor state of health, the initial dose should be reduced to mitoxantrone 12 mg/m$^2$ or as appropriate for the haematological status.

For each repeated application of Onkotrone Concentrate, the dose should be adjusted in each case in accordance with the individual patient's progress and the extent and duration of myelosuppression.

If leucocyte and platelet counts have returned to normal after 21 days then the original dose can be repeated.

*The following general recommendations can be given for dose adjustment in the treatment of advanced breast cancer, non-Hodgkin's lymphoma and hepatocellular carcinoma:*

| **Lowest value (nadir) of leucocytes and platelets (as a rule, 6 to 15 days after application)** | **Return to normal** | **Recommended dosage** |
|---|---|---|
| More than 1.5 x $10^9$/l leucocytes and more than 50 x $10^9$/l platelets | 21 days or less | As previous dose or increase by 2 mg/m$^2$ if myelosuppression is not considered adequate |
| More than 1.5 x $10^9$/l leucocytes and more than 50 x $10^9$/l platelets | More than 21 days | Wait for return to normal, then as previous dose |
| Less than 1.5 x $10^9$/l leucocytes or less than 50 x $10^9$/l platelets | Independent of return to normal | Reduction of the previous dose by 2 mg/m$^2$ after recovery |
| Less than 1.0 x $10^9$/l leucocytes or less than 25 x $10^9$/l platelets | Independent of return to normal | Reduction of the previous dose by 4 mg/m$^2$ after recovery |

Combined use of Onkotrone Concentrate with other cytostatic agents may require dose modifications depending on the condition of the patient. This must be taken into consideration during the first induction course and/or subsequent treatment courses.

If Onkotrone Concentrate is combined with other myelotoxic agents, it is advisable to reduce the initial dose recommended for monotherapy by 2 to 4 mg/m$^2$ mitoxantrone. Reference to published literature should be made for information on dosage modification/administration.

**2. Acute Non-Lymphocytic Leukaemia**

For the induction treatment of acute leukaemia in adults, it is recommended to use a dose of mitoxantrone of 12 mg/m$^2$ for five consecutive days (total dose 60 mg/m$^2$). Higher remission rates can be achieved after a daily dose of 12 mg/m$^2$ for five days. The higher dosage, however, should only be administered when the condition of the patient permits.

Combination of mitoxantrone with other cytotoxic agents has been successful in the treatment of acute non-lymphocytic leukaemia. Most clinical experience has been with mitoxantrone combined with cytosine arabinoside. Mitoxantrone 10-12 mg/m$^2$ i.v. for 3 days combined with continuous infusion cytosine arabinoside 100 mg/m$^2$ i.v. for 7 days have been given for induction.

In patients who were refractory to conventional chemotherapy or who had relapsed, mitoxantrone in combination with etoposide has demonstrated efficacy.

The use of any cytotoxic agents, including cytosine arabinoside or etoposide, with mitoxantrone may cause greater myelosuppression than when mitoxantrone is used alone.

Dose modification or prolongation of the dosage interval should be adjusted according to the clinical condition of the patient and the haematological and non-haematological parameters. Reference to published literature should be made for information on dosage modification/administration.

**Mode and duration of application**

Onkotrone Concentrate should only be administered by experienced oncologists.

**Onkotrone should not be given intrathecally**

*Intravenous application:*
Onkotrone Concentrate should only be administered as a slow intravenous infusion over not less than 5 min. Onkotrone Concentrate should be diluted to at least 50 ml, and injected slowly into a fast-running intravenous infusion. Isotonic saline or a 5% glucose solution are suitable carrier solutions and diluents. Onkotrone should not be mixed with other drugs in the same solution.

Onkotrone Concentrate can be infused for short periods (15-30 min). The calculated dose should be diluted with 50 to 100 ml of one of the above mentioned infusion solutions.

If extravasation occurs, the administration should be stopped immediately and restarted using a different vein. To date, only isolated cases of severe local reactions (necroses) have been described due to extravasation.

It is not recommended to give Onkotrone Concentrate inter-arterially.

## 4.3 Contraindications

Onkotrone Concentrate must not be used in cases of known hypersensitivity to the active ingredient.

Data are not available to support the use of Onkotrone Concentrate in childhood malignancy and therefore it should not be used.

Onkotrone Concentrate should not be administered to patients suffering from severe hepatic insufficiency, defined as a serum bilirubin 60 µmol/l or greater.

Onkotrone Concentrate must not be used during pregnancy or lactation.

**Onkotrone Concentrate should not be given via the intrathecal route.**

## 4.4 Special warnings and precautions for use

**Onkotrone Injections** should be applied with caution in patients suffering from pancytopenia or septicaemia. This also applies in the case of severe hepatic and/or renal insufficiency.

Cases of functional cardiac changes, including congestive heart failure decreases in left ventricular ejection fraction have been reported. Risk factors such as prior treatment with anthracyclines, prior mediastinal/thoracic radiotherapy, or pre-existing heart disease may increase the risk of cardiotoxicity. It is recommended that patients in these categories are treated with Onkotrone Injections at full cytotoxic dosage and schedule. However, added caution is required in these patients and careful regular cardiac examinations are recommended from the initiation of treatment.

As experience of prolonged treatment with mitoxantrone is presently limited, it is suggested that the cardiac examinations also be performed in patients without identifiable risk factors during therapy exceeding a cumulative dose of 160 mg/m$^2$.

Secondary acute myelogenous leukaemia (AML) has been reported in cancer patients treated with topoisomerase II inhibitors like mitoxantrone. The occurrence of refractory secondary leukaemia is more common when topoisomerase II inhibitors are given with other DNA-damaging antineoplastic agents and/or radiotherapy, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of topoisomerase II inhibitors have been escalated. The incidence of these events has not been quantified.

Haematological blood parameters must be monitored before each application of **Onkotrone Injection** as well as at least once during each treatment cycle.

## 4.5 Interaction with other medicinal products and other forms of interaction

Combination treatment with other antineoplastic drugs are more likely to result in potent toxic effects, in particular, increased myelotoxic and cardiotoxic effects are to be expected.

## 4.6 Pregnancy and lactation

During Onkotrone Concentrate treatment and for at least six months after termination of chemotherapy, effective contraception should be practised by patients of reproductive age, or either sex. Patients' partners capable of conception should also avoid pregnancy for 6 months after the patients' treatment cessation.

*Use during pregnancy and lactation:*
Onkotrone Concentrate is contraindicated during pregnancy and lactation.

No animal reproductive studies have been performed, however, mitoxantrone is expected to be embryotoxic and/or teratogenic.

## 4.7 Effects on ability to drive and use machines

None known.

## 4.8 Undesirable effects

Bone marrow depression may occur during Onkotrone Concentrate treatment even in the therapeutic dose range. Leucocytes are particularly susceptible. In patients who have previously undergone chemotherapy and/or radiotherapy as well as in patients in a generally poor state of health, marked bone marrow depression can occur. The leucocyte count nadir is generally observed between 6 and 15 days after mitoxantrone administration. Subsequently, the bone marrow and haematological state recover which as a rule is completed by 21 days after administration. Severe thrombocytopenia and very low haematocrit are seldom observed.

Topoisomerase II inhibitors, including mitoxantrone, in combination with other antineoplastic agents, have been associated with the development of acute leukaemia.

Nausea and vomiting can occur temporarily. They are in most cases of mild to moderate severity. If alopecia occurs it is usually mild and usually reversible on discontinuation of treatment.

Cardiac side-effects such as transient ECG alterations, acute arrhythmias, reduced left-ventricular output as well as cases of cardiac insufficiency can occur after administration of Onkotrone Concentrate. These cardiac phenomena are observed particularly in high risk patients, as defined in 4.4 above.

Patients with cardiac insufficiency generally respond well to a supportive treatment with cardiac glycosides and/or diuretic agents.

Occasionally, stomatitis and/or mucositis can occur (more frequent and pronounced during treatment of leukaemia).

Rarely, hypersensitivity reactions occur which may appear as acute allergic generalised reactions (anaphylaxis) in exceptional cases.

Side-effects such as loss of appetite, diarrhoea, abdominal pain, constipation, gastrointestinal bleeding, tiredness and weakness, amenorrhoea, fever, dyspnoea, and non-specific neurological side-effects (somnolence, confusion, anxiety, mild paraesthesia) are occasionally observed.

Liver enzyme, serum creatinine and blood urea values may alter temporarily in individual cases. Marked pathological alterations of liver enzyme values and an impairment of liver function can occasionally occur in patients with acute leukaemia.

Onkotrone Concentrate causes a blue-green coloration of the urine one to two days after administration. Blue coloration of the skin and nails has been reported occasionally. Nail dystrophy or reversible blue coloration of the sclerae may be seen very rarely.

## 4.9 Overdose

*Symptoms of intoxication:*
There is no known antidote for Onkotrone Concentrate. Haemopoietic, gastrointestinal, hepatic or renal toxicity may be seen depending on the dosage given and physical condition of the patient. Onkotrone Concentrate cannot be removed by dialysis. The usual supportive measures (maintenance of fluid and electrolyte balance, monitoring of renal and hepatic function, cardiovascular monitoring, prophylaxis against infection) should be carried out.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Although the precise mechanism of action of mitoxantrone has not yet been completely elucidated, it is a DNA-reactive agent. It acts cytocidally on both proliferating and non-proliferating cells suggesting activity against rapidly proliferating and slow growing neoplasms.

## 5.2 Pharmacokinetic properties

Pharmacokinetic studies in patients following intravenous administration of mitoxantrone demonstrated a triphasic plasma clearance. Distribution to tissues is rapid and extensive. Elimination of the drug is slow with a mean half-life of 12 days (range 5-18) and persistent tissue concentrations. Similar estimates of half-life were obtained from patients receiving a single dose of mitoxantrone every 21 days and patients dosed on 5 consecutive days every 21 days.

Mitoxantrone is excreted via the renal and hepatobiliary systems. Only 20-32% of the administered dose was excreted within the first five days after dosing (urine 6-11%, faeces 13-25%). Of the material recovered in the urine 65% was unchanged mitoxantrone and the remaining 35% is primarily comprised of two inactive metabolites and their glucuronide conjugates. Approximately two thirds of the excretion occurred during the first day.

## 5.3 Preclinical safety data

*Acute toxicity*
The acute toxicity of mitoxantrone has been investigated in mice and rats following intravenous, intraperitoneal and subcutaneous application.

*Chronic toxicity:*
Animal experiments to determine chronic toxicity are characterised by the predominance of bone marrow depletion and secondary infections. The following additional species specific toxicities have been observed:

In dogs, diarrhoea, vomiting, salivation, skin lesions, swelling of the limbs, inactivity and in rats, loss of weight, meteorism, ascites, moderately increased hepatic and cardiac enzyme values and impairment of renal function.

To determine the cardiotoxic effects of mitoxantrone, several toxicological tests were carried out in rats, dogs, rabbits and other animal species. It has been demonstrated that mitoxantrone, using an intermittent dosage regimen, does not cause cardiomyopathy or cardiotoxicity, which are typical of anthracyclines. Mitoxantrone treatment can cause reversible damage to the cardiac myocytes in contrast to the damage caused by anthracyclines which is irreversible.

Mitoxantrone has been shown to be mutagenic in a variety of tests, and therefore, may be considered a potential carcinogen in the absence of suitable test data.

No animal reproductive studies have been performed, however, mitoxantrone is expected to be embryotoxic and/or teratogenic.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium chloride
Sodium acetate
Acetic acid
Water for Injections

## 6.2 Incompatibilities

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

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

## 6.3 Shelf Life

3 years unopened.

In-use shelf life: Chemical and physical in-use stability has demonstrated for 8 hours at 2-8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user but should not exceed 8 hours.

For single use only.

## 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 I injection vial with rubber stopper and aluminium flange cap.

*Pack Sizes:*
1 injection vial containing 20mg mitoxantrone in 10 ml injection solution.
1 injection vial containing 25mg mitoxantrone in 12.5 ml injection solution.
1 injection vial containing 30mg mitoxantrone in 15 ml injection solution.

## 6.6 Instructions for use and handling

*Intravenous administration:*
Onkotrone Concentrate should only be administered as a slow intravenous infusion over not less than 5 min. Onkotrone Concentrate should be diluted to at least 50 ml, and injected slowly into a fast-running intravenous infusion. Isotonic saline or a 5% glucose solution are suitable carrier solutions and diluents. Onkotrone should not be mixed with other drugs in the same solution.

Onkotrone Concentrate can be infused for short periods (15-30 min). The calculated dose should be diluted with 50 to 100 ml of one of the above mentioned infusion solutions.

If extravasation occurs, the administration should be stopped immediately and restarted using a different vein. To date, only isolated cases of severe local reactions (necroses) have been described due to extravasation.

It is not recommended to give Onkotrone Concentrate intra-arterially.

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

Care should be taken when handling Onkotrone Concentrate 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 Concentrate can cause staining. If contact of Onkotrone Concentrate 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 Concentrate 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 Concentrate contaminated items (e.g. 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

ASTA Medica Limited
168 Cowley Road
Cambridge
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## 8 MARKETING AUTHORISATION NUMBER

PA 705/13/1

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th June 2001

## 10 DATE OF REVISION OF THE TEXT

March 2004