1 ONKOTRONE (2mg/mL concentrate for injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mitoxantrone hydrochloride 2.328mg/mL (equivalent to mitoxantrone 2mg/mL) of solution for injection.

3 PHARMACEUTICAL FORM

Concentrate for injection.

ONKOTRONE concentrated Injection is a clear, dark blue liquid with a pH of 3.0 – 4.5.

Mitoxantrone hydrochloride is a hygroscopic dark blue solid.

For the full list of excipients, see Section 6.1.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ONKOTRONE is indicated for the treatment of:

- Locally advanced or metastatic carcinoma of the breast
- Non-Hodgkin's lymphoma
- Adult acute non-lymphocytic leukaemia (ANLL)
- Chronic myelogenous leukaemia in blast crisis.

4.2 Dose and method of administration

The dose should be adjusted to each patient carefully. Doses greater than 140mg/m^2 are not recommended, particularly as a single bolus injection. Such administrations have caused fatal overdose as a result of severe leucopenia and infection.

Use in Children

Experience in paediatric patients is limited.

Intrathecal use

Safety for intrathecal use of mitoxantrone has not yet been established.

Breast cancer and Lymphoma

Single-agent therapy

The recommended initial dosage for use as a single agent is 14mg/m^2 of body surface area, given as a single intravenous dose, which may be repeated at 21 day intervals.

A lower initial dose (12mg/m^2 or less) is recommended in patients with inadequate marrow reserves due to prior therapy or poor general condition.

Dosage modification and timing of subsequent dosing should be determined by clinical judgement depending on the degree and duration of myelosuppression. If 21 day white blood cell and platelet counts have returned to adequate levels, prior doses can usually be repeated. The following table indicates a guide to dosing based on myelosuppression for the treatment of breast cancer and non-Hodgkin's lymphoma.

Lowest value (nadir) of leucocytes and thrombocytes (cell/mm³)	Time to recovery	Subsequent dosing
> 1500 leucocytes and > 50,000 (cells/mm³) thrombocytes	21 days or less	As previous dose or increase by 2mg/m² if the degree of myelosuppression indicates that a higher dose can be tolerated
> 1500 leucocytes and > 50,000 thrombocytes	More than 21 days	Wait for return to normal, and then as previous dose
< 1500 leucocytes or < 50,000 thrombocytes	Any duration	Reduction of the previous dose by 2mg/m² after recovery of blood counts
< 1000 leucocytes or < 25,000 thrombocytes	Any duration	Reduction of the previous dose by 4mg/mg² after recovery of blood counts

Combination therapy
Mitoxantrone has been given in various combination regimens with the following cytotoxic agents for the treatment of breast cancer and lymphomas: cyclophosphamide, fluorouracil, vincristine, vinblastine, bleomycin, methotrexate (standard dose or 200mg/m² with leucovorin rescue) and glucocorticoids.

For the combination of mitoxantrone with other myelosuppressive agents, it is advisable to reduce the initial dose of mitoxantrone recommended for monotherapy by 2 to 4mg mitoxantrone/m² of body surface area. In further treatment cycles, the mitoxantrone dose should be similarly tailored to individual progress and to the duration and degree of myelosuppression.

Long-term survival data for non-Hodgkin's lymphoma are as yet inadequate to establish comparability between combinations containing mitoxantrone and similar combinations containing doxorubicin.

Leukaemia
Combination therapy
Mitoxantrone, together with cytosine arabinoside, has been used successfully for the treatment of both first and second line patients with acute non-lymphocytic leukaemia. For induction, the recommended dose is 10 to 12mg/m² mitoxantrone for three days and 100mg/m² of cytosine arabinoside for 7 days (the latter given as a continuous 24hr infusion).

If a second course is indicated, then this is given with the same combination at the same daily dosage levels but with the mitoxantrone given for only 2 days and cytosine arabinoside for only 5 days.

If severe or life-threatening non-haematological toxicity is observed during the first induction course, the second induction course should be withheld until the toxicity clears.

Paediatric usage
Experience in paediatric patients is limited.

Single agent dosage for acute non-lymphocytic leukaemia or chronic myelogenous leukaemia in blast crisis
The recommended dose for induction is 12mg/m² of body surface area, given as a single intravenous dose daily for 5 consecutive days (total 60mg/m²). In clinical studies, with this dosage regimen, patients who achieved a complete remission did so with the first induction course.

Re-induction upon relapse may be attempted with mitoxantrone using the same dose regimen.

Directions for Use

ONKOTRONE vials contain an overage to allow for withdrawal of the required volume.

Mitoxantrone should be administered slowly as an intravenous infusion over a period of 15 - 30 minutes (not less than 5 minutes).

ONKOTRONE should be diluted to at least 50mL with either sodium chloride for injection or 5% glucose for injection. This solution should be introduced slowly into the tube of a freely running intravenous infusion of sodium chloride for injection or 5% glucose for injection over not less than 3 - 5 minutes. Administration should be followed with a flush of the appropriate diluent.

If extravasation occurs, the administration should be stopped immediately and restarted in another vein.

4.3 Contraindications

ONKOTRONE should not be used in patients with:

- Known hypersensitivity to mitoxantrone, or to any of the excipients in Section 6.1
- Pregnancy, lactation
- Severe myelosuppression due to previous treatment with other cytotoxic agents or radiotherapy: treatment with mitoxantrone should not be initiated until bone marrow has recovered
- Patients who have received prior substantial anthracycline therapy with abnormal cardiac function prior to the initiation of therapy (see Section 4.4)
- Severe hepatic impairment
- For intraarterial, subcutaneous, intramuscular or intrathecal administration due to associated toxicities.

4.4 Special warnings and precautions for use

ONKOTRONE injection concentrate should be administered only under constant supervision by physicians experienced in therapy with cytotoxic agents and only when potential benefits of **ONKOTRONE** therapy outweigh the possible risks. Appropriate facilities should be available for adequate management of complications should they arise.

Full blood counts must be checked before each administration of **ONKOTRONE** as well as undertaken serially during a course of treatment. Dosage adjustments may be necessary based on these counts (see Section 4.2).

Systemic infections should be treated concomitantly with, or just prior to, commencing therapy with **ONKOTRONE**.

Instructions to patients

Patients should be instructed to inform their doctor of any prior abnormal heart conditions. Patients should also be advised of the signs and symptoms of myelosuppression.

Patients should be advised to expect a blue-green colouration to the urine for up to 24 hours after **ONKOTRONE** administration. Bluish discolouration of the sclera may also occur.

Administration

ONKOTRONE is not indicated for subcutaneous, intramuscular, or intra-arterial injection. There have been reports of local/regional neuropathy, some irreversible, following intra-arterial injection.

ONKOTRONE must not be given by intrathecal injection. 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 neurological sequelae, and paralysis with bowel and bladder dysfunction (see Section 4.3).

Haematological

Since **ONKOTRONE** produces myelosuppression, it should be used with caution in patients in poor general condition or with pre-existing myelosuppression due to any cause. There is high incidence of bone marrow depression primarily of leucocytes, requiring careful haematological monitoring or patients with severe infections at the florid stage. The haemotological blood parameters must be monitored before each application of **ONKOTRONE** as well as at least once during each treatment cycle.

Following recommended doses of **ONKOTRONE**, leucopenia is usually transient, reaching the nadir at about 10 days after dosing, with recovery usually occurring by the twenty-first day. White blood cell counts as low as 1.5×10^9/L may be expected following therapy, but white cell counts rarely fall below 1.0×10^9/L at recommended dosages. Red blood cells and platelets should also be monitored since depression of these elements may also occur. Haematological toxicity may require reduction of dose or suspension or delay of **ONKOTRONE** therapy.

Topoisomerase II inhibitors, including mitoxantrone, when used alone or concomitantly with other antineoplastic agents and/or radiotherapy, have been associated with the development of Acute Myeloid Leukaemia (AML), Acute Promyelocytic Leukaemia (APL) or Myselodysplastic Syndrome (MDS).

ONKOTRONE has been associated with the development of secondary AML in humans (see Section 4.8).

Renal function

Patients with impared renal failure have not been studied. However, as mitoxantrone undergoes limited renal excretion and extensive tissue binding, it is unlikely that the therapeutic effect or toxicity in these patients would be reduced by peritoneal dialysis or haemodialysis. **ONKOTRONE** should be used with caution in patients with severe renal insufficiency.

Cardiovascular

Cases of functional cardiac changes, including congestive heart failure and decreases in left ventricular ejection fraction have been reported during **ONKOTRONE** therapy. These cardiac events have most commonly occurred in patients who have had prior treatment with anthracyclines, prior mediastinal radiotherapy or with pre-existing heart disease, indicating a possible increased risk of cardiotoxicity in such patients. It is therefore recommended that regular cardiac monitoring also be performed in these patients, taking into account the extent to which individual patients have been exposed to these cardiac risk factors.

A small proportion of endomyocardial biopsy reports have demonstrated changes consistent with anthracycline toxicity in patients who had not received prior anthracyclines. Based on current experience, it is recommended that cardiac monitoring also be performed in patients without pre-existing cardiac risk factors before initiation of therapy and during therapy exceeding $140 mg/m^2$ of mitoxantrone.

In patients with one or more of these risk factors, or in the case of combination of **ONKOTRONE** with other cardiotoxic agents, the treatment must be carefully monitored, with regular controls of cardiac function, and adjustment of the dose where necessary.

When a total cumulative mitoxantrone dose of 160mg/m² has been reached in patients with no risk factors, regular control of cardiac function should be carried out.

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

Hepatic

Careful supervision is recommended when treating patients with hepatic insufficiency. Although adequate data on the use of mitoxantrone in patients with hepatic dysfunction are not yet available, the pharmacokinetic profile suggests that clearance of mitoxantrone in such patients may be reduced and dosage may need to be adjusted accordingly (see Section 4.3). **ONKOTRONE** should be used with extreme caution in jaundiced patients.

ONKOTRONE should be used with caution in patients with severe hepatic insufficiency. Liver function should be monitored regularly before and during treatment.

Uricacidaemia

Hyperuricaemia may occur as a result of rapid lysis of tumour cells by **ONKOTRONE**. Serum uric acid levels should be monitored and hypouricaemic therapy instituted prior to the initiation of antileukaemic therapy.

Paediatric use

Experience in paediatrics patients is limited.

Geriatric use

Monitoring for toxicities and the need for dose adjustment should reflect the higher frequency of decreased hepatic, renal, cardiac or other organ function and concomitant diseases or other medicine therapy in this population.

Effects on laboratory tests

Animal data suggest that if used in combination with other antineoplastic agents, additive myelosuppression may be expected. This has been supported by available clinical data on combination regimens (see Section 4.2/Combination therapy).

4.5 Interaction with other medicines and other forms of interaction

Planned co-administration or sequential administration of other substances or treatments that could increase the likelihood or severity of toxic effects (by means of pharmacodynamics or pharmacokinetics interactions) requires careful individual assessment of the expected benefit and the risks. Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.

It is recommended that **ONKOTRONE** not be mixed in the same infusion with other medicines as specific compatibility data are not available.

ONKOTRONE must not be mixed in the same infusion as heparin as a precipitate may form.

ONKOTRONE must not be administered through the same intravenous line as other medicines.

When used in combination with other antineoplastic agents, more potent toxic effects, especially an increased myelotoxic and cardiotoxic effect are expected.

When used in combination regimens, the initial dose of **ONKOTRONE** should be reduced by 2 - 4mg/m² below the dose recommended for single-agent usage (see Section 4.2).

Combination therapy with other cytotoxic medicines and/or radiation therapy has been associated with t-AML and myelodysplastic syndrome.

The immunosuppressive effects of mitoxantrone can be expected to reduce the response to vaccines. Use of live vaccines may lead to vaccine-induced infection.

Cyclosporine may reduce mitoxantrone clearance rate in patients with AML.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category D)

Medicines which have caused, are suspected to have caused, or maybe expected to cause, an increased incidence of human malformations or irreversible damage. These medicines may also have adverse pharmacological effects.

There is no information on the use of mitoxantrone in pregnancy. Therefore mitoxantrone should not be used in pregnant women or those likely to become pregnant unless the expected benefit outweighs any potential risk.

If the patient becomes pregnant during treatment with mitoxantrone, medical consultation about the risk of damaging effects to the embryo associated with the treatment should occur. The effects of mitoxantrone can damage the genotype and influence the development of the embryo.

As with other antineoplastic agents, patients and their partners should use effective methods of contraception and be advised to avoid conception for at least six months after cessation of therapy.

It is unknown if mitoxantrone can cross the placental barrier.

Breast-feeding

Mitoxantrone is excreted in human milk and significant concentrations (18ng/mL) have been reported for 28 days after last administration. Because of the potential for serious adverse reactions in infants from mitoxantrone, breastfeeding should be discontinued before stating treatment.

Fertility

The effects of mitoxantrone on human fertility have not been established. No adequate studies have been conducted in animals to determine the effect of mitoxantrone on fertility and irreversible infertility.

4.7 Effects on ability to drive and use machines

Patients undergoing treatment with **ONKOTRONE** may experience undesirable effects see Section 4.8 (including, e.g., confusion and fatigue) which could affect the ability to drive or use machines. The decision to drive or operate machinery should be made on an individual basis.

4.8 Undesirable effects

When used as a single injection every three weeks in the treatment of solid tumours and lymphomas, the most commonly encountered side effects are nausea and vomiting, although in the majority of cases these are mild and transient. Alopecia may occur, but is most frequently of minimal severity and reversible on cessation of therapy.

In patients with leukaemia, the pattern of side effects is generally similar, although there is an increase in both frequency and severity, particularly of stomatitis and mucositis. Nevertheless, overall, patients with leukaemia tolerate treatment with **ONKOTRONE** well.

Common reactions
INFECTIONS AND INFESTATIONS: Sepsis and infection.

GASTROINTESTINAL: Nausea, vomiting, stomatitis and/or mucositis. In the majority of cases these are mild (WHO Grade 1) to moderate severity and transient. In some cases the stomatitis and mucositis may be more frequent and pronounced during the treatment of leukaemia.

DERMATOLOGICAL: Alopecia, most frequently of minimal severity on cessation of therapy.

HAEMATOLOGICAL: Bone marrow failure, pancytopenia, febrile neutropenia, neutropenia, myelosuppression, especially leucopenia. Thrombocytopenia and anaemia are less common.

RENAL: **ONKOTRONE** may impart a blue-green colour to the urine for 1-2 days after administration.

Less common reactions
GASTROINTESTINAL: Diarrhoea, constipation, anorexia, gastrointestinal bleeding, abdominal pain, abdominal tenderness, pancreatitis and altered taste.

RESPIRATORY: Dyspnoea and interstitial pneumonitis.

LOCAL: Phlebitis. Extravasation at the infusion site has been reported, which may result in erthema, swelling, pain, burning and/or blue discolouration of the skin. Tissue necrosis following extravasation has been reported rarely.

GENERAL: Hypersensitivity reactions, allergic reaction (hypotension, urticaria, anaphylaxis) has been reported. Fever, fatigue and weakness, and nonspecific neurological side effects such as somnolence, confusion, anxiety and mild paraesthesia. Tumour lysis syndrome (characterised by hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia) has been observed rarely during single agent chemotherapy with mitoxantrone, as well as during combination chemotherapy.

DERMATOLOGICAL: Alopecia, rash, nail disorder, pigmentation and onycholysis.

HEPATIC: Hepatotoxicity. Increased liver enzyme levels and elevated bilirubin levels have been reported occasionally.

RENAL: Elevated serum creatinine and blood urea nitrogen levels have been reported occasionally.

OPHTHALMIC: Reversible blue colouration of the sclerae has been reported.

PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS: Foetal growth restriction.

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: Amenorrhea and Oligospermia.

Severe or life-threatening reactions
CARDIOVASCULAR: Cardiomyopathy, cardiovascular effects include cardiac failure, decreased left ventricular ejection fraction (determined by ECHO or MUGA scan), ECG changes and acute arrhythmia. Congestive heart failure has been reported. Such cases have generally responded well to treatment with digitalis and/or diuretics.

Bradycardia, tachycardia and chest pain have been reported.

In patients with leukaemia there is an increase in the frequency of cardiac events. The direct role of mitoxantrone in these cases is difficult to assess, since some patients had received prior therapy with anthracyclines and since their clinical course is frequently complicated by anaemia, fever, sepsis and intravenous fluid therapy.

HAEMATOLOGICAL: Some degree of leucopenia is to be expected following recommended doses of **ONKOTRONE** in solid tumors; however, suppression of white blood cell counts below 1.0 x 109/L is infrequent. With dosing every 21 days, leucopenia is usually transient, reaching its nadir at about ten days after dosing, with recovery usually occurring by the twenty-first day. Thrombocytopenia can occur and anaemia occurs less frequently. Myelosuppression may be more severe and prolonged in patients with solid tumors, who have had extensive prior chemotherapy or radiotherapy, or in debilitated patients. Acute Promyelocutic Leukaemia (APL) has been reported.

Secondary AML/acute myelodysplastic syndrome (AMS) has been reported following chemotherapy with various DNA topoisomerase II poisons, including mitoxantrone. In one study a 5% incidence of secondary AML/AMS was reported after treatment with mitoxantrone and methotrexate, mitoxantrone was suspected as the causative agent. Features of the AML include a latency period of < three years, short preleukaemia phase and nonspecific cytogenic alterations.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms
In the case of acute or chronic over dosage, the observed side effects are amplified including renal, hepatic and cardiac toxicities. The extent of bone marrow depression, at the extreme agranulocytosis accompanied by necrotising angina and critical thrombocytopenia, determines the further course in acute and chronic overdosage.

Ulceration of the mouth and gastrointestinal tract, haemorrhagic enterocolitis with massive bleeding, diarrhoea and persistent signs of renal and hepatic toxicity can occur.

If aplasia of the bone marrow occurs as a result of acute overdosage with mitoxantrone, it will, from existing experience, persist longer (approx 3 weeks).

In patients with acute leukaemia, it can result in pronounced stomatitis in isolated cases. Appropriate measures for prophylaxis and treatment should therefore be taken.

In isolated cases, acute cardiac symptoms of different severity are possible.

Toxicity may be delayed and life-threatening e.g. myelosuppression.

Treatment

A specific antidote to mitoxantrone is not known. Mitoxantrone is rapidly eliminated from the blood plasma and shows high tissue affinity. Therefore, it cannot be eliminated by dialysis. To counteract agranulocytosis and thrombocyte, granulocyte colony-stimulating factor and thrombocyte concentrates may be necessary.

Haematological support may be required during prolonged periods of bone marrow depression, and infection prophylaxis with antibiotics may be required. The usual supportive measures (maintenance of fluid and electrolyte balance, monitoring of renal and hepatic functions, strict cardiovascular monitoring etc) should be carried out. Every overdosage requires careful monitoring of the clinical findings to identify possible delayed complications.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group	Antineoplastic and immunomodulating agents, Antineoplastic agents, Cytotoxic antibiotics and related substances, Anthracyclines and related substances.
ATC code	L01DB07.

Mitoxantrone hydrochloride is a cytostatic agent that has shown substantial anti-tumour activity in the treatment of a variety of tumors. It is a DNA-reactive agent, but the precise mechanism of the tumour destroying effect has not yet been completely elucidated. Mitoxantrone acts both on proliferating and non-proliferating cells. It is a cell cycle (phase) non-specific substance.

The main toxic effects of mitoxantrone in animals at doses within the human therapeutic range are reversible myelosuppression (predominantly leucopenia, with anaemia and thrombocytopenia being less severe) and lymphocytic depletion of the lymphoid organs. In continuous daily dosage schedules, gastrointestinal haemorrhage and congestion were observed, but these were not seen in intermittent schedules as used clinically. Studies in dogs using mitoxantrone in combination with other antineoplastic agents indicated that additive myelosuppression might be expected from combination therapy.

Toxicological tests have been carried out with mitoxantrone in order to study its cardiotoxic effects. In studies in dogs and monkeys, doxorubicin given at equileucopenic doses was used as a positive control for anthracycline-induced cardiomyopathy. Dogs given mitoxantrone and untreated control dogs showed slight dilatation of the sarcoplasmic reticulum, which regressed over time. In monkeys, clinical signs of congestive heart failure were observed in animals given doxorubicin but not in those given mitoxantrone. In the doxorubicin-treated monkeys, myocyte changes were characteristic of degeneration, while the myocyte changes in monkeys given mitoxantrone suggested cellular regeneration and repair. In rats, there was no evidence of the progressive cardiomyopathy characteristic of anthracyclines.

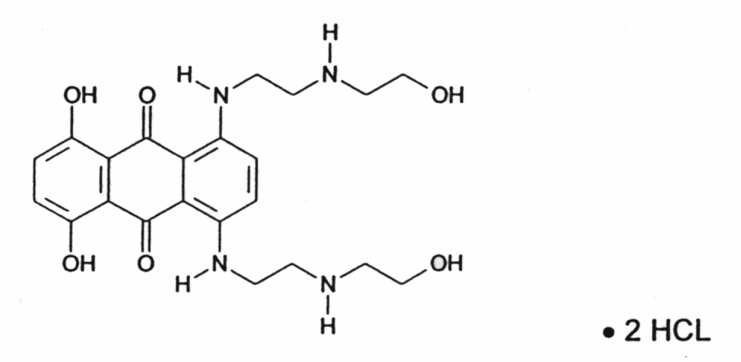
Mitoxantrone hydrochloride is a synthetic anthracenedione.

Chemical name:	1,4-dihydroxy-5,8-bis-[2-(2-hydroxyethylamino)-ethylamino]-9,10-anthraquinone dihydrochloride.
Chemical formula:	$C_{22}H_{28}N_4O_6.2HCl$

Molecular weight: 517.4

CAS number: 70476-82-3

Chemical structure:



5.2 Pharmacokinetic properties

Mitoxantrone is rapidly eliminated from blood plasma after intravenous application and is extensively distributed to tissues (apart from the CNS) and has therefore a large distribution volume. A triphasic plasma clearance is observed. Elimination is slow with a terminal half-life of over 12 days (range 5 – 18). Administration schedules of daily for 5 days and a single dose every 3 weeks resulted in similar estimates of the half-life. Plasma accumulation of mitoxantrone was not apparent on either schedule.

Excretion by the biliary and faecal route appears to be the major pathway of elimination for mitoxantrone. The renal excretion is of secondary importance; only 6 - 11% of the dose is recovered in the urine within 5 days after mitoxantrone administration, with 65% of this being unchanged mitoxantrone. The remaining 35% consisted primarily of two inactive metabolites, the mono- and di-carboxylic acid derivatives and their glucuronide conjugates.

One study found that a mean of 18.3% (13.6 – 24.8%) of a dose of 14C-labelled mitoxantrone was excreted via the faeces over 5 days.

Mitoxantrone does not cross the blood brain barrier or the placental barrier. Distribution into testes is relatively low.

One study found that the protein binding of mitoxantrone was 78% at concentrations ranging from 26 to 455ng ^{14}C-mitoxantrone/mL pooled human plasma. The extent of binding was independent of concentration.

No significant difference in the pharmacokinetics of mitoxantrone was observed in patients with moderately impaired hepatic function (serum bilirubin 1.3 to 3.4mg/dL) as compared to 16 patients without hepatic dysfunction. Studies in 4 patients with severe hepatic impairment (bilirubin greater than 3.4mg/dL) suggest that these patients have a lower total body clearance and a larger area under the curve (AUC) than other patients receiving a comparable dose.

In animals, pharmacokinetic studies with radiolabelled mitoxantrone indicate rapid, dose-proportional distribution into most tissues. Biliary excretion is the major route of elimination, with the urine and bile of the rat containing the same metabolites as those present in human urine. There is no significant absorption of mitoxantrone in animals following oral administration.

5.3 Preclinical safety data

See Section 4.4/Effects on Laboratory tests, and Section 5.1.

Carcinogenicity/Mutagenicity

Animal studies have not demonstrated teratogenic activity due to mitoxantrone treatment. Decreased foetal body weight noted in high dose rats (0.2mg/kg/day) and an increased incidence of premature delivery noted in rabbits (0.01 to 0.05mg/kg/day) were attributed to maternal toxicity.

In a lifetime study in rats, there was a possible association between the administration of mitoxantrone and the development of malignant neoplasia.

Mitoxantrone caused point mutations, DNA damage and sister chromatid exchanges *in vitro*. Lifetime studies in mice and rats showed no residual clastogenic effect. Mitoxantrone did not induce cell transformation in mammalian cells *in vitro*.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium acetate, acetic acid-glacial and water for injection.

6.2 Incompatibilities

ONKOTRONE must not be mixed in the same infusion as heparin as a precipitate may form.

It is recommended that **ONKOTRONE** not be mixed in the same infusion with other medicines, as specific compatibility data are not available.

6.3 Shelf life

3 years from date of manufacture stored at or below 25°C
7 days opened stored at or below 25°C.

After Reconstitution

Potency is maintained for 2 days stored at or below 25°C; however, to reduce microbial hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2 - 8°C for not more than 24 hours.

6.4 Special precautions for storage

Unopened Vials: Store below 25°C. Do not freeze. Protect from light.

6.5 Nature and contents of container

ENDOXAN is available in vials: 10mg/5mL, 20mg/10mL, 25mg/12.5mL, 30mg/15mL.

Not all presentations are necessarily marketed.

6.6 Special precautions for disposal and other handling

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

Pharmaceutical precautions

Care should be taken to avoid contact of **ONKOTRONE** with the skin, mucous membranes or eyes. The use of goggles, gloves and protective gowns is recommended during preparation and administration. To reduce the possibility of spillages and splashes when removing ONKOTRONE form the vial, it is recommended that a 20 gauge needle, or one with a narrower bore, be used.

ONKONTRONE can cause staining.

Skin accidentally exposed to **ONKOTRONE** should be rinsed copiously with warm water and if the eyes are involved, standard irrigation techniques should be used. Equipment and spills on environmental surfaces may be cleaned up by using an aqueous solution of calcium hypochlorite (5.5 parts calcium hypochlorite in 13 parts by weight of water for each 1 part by weight of **ONKOTRONE**). Absorb the remaining solutions with gauze or towels and dispose of these in a safe manner. Appropriate safety equipment such as goggles and gloves should be worn while working with calcium hypochlorite solutions.

ONKOTRONE does not contain an antimicrobial preservative. Although the preparation itself does have some antimicrobial efficacy, the injection should be used as soon as possible after opening and any residue discarded.

ONKOTRONE must not be mixed in the same infusion as heparin since a precipitate may form. It is recommended that **ONKOTRONE** not be mixed in the same infusion with other medicines as specific compatibility data are not available.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

ONKOTRONE *is distributed in New Zealand by:*

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

ONKOTRONE *is distributed in Australia by:*

Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
24 February 2000.

10 DATE OF REVISION OF THE TEXT

22 October 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	*Less common reactions/GASTROINTESTINAL*: addition of pancreatitis.

Based on Australian PI amended 28 August 2015; and CCSI 420 2015 FEB16.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.