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Baxter

PACKAGE LEAFLET: INFORMATION FOR THE PATIENT

Onkotrone Injection

2mg/ml concentrate for solution for infusion 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 or pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effect not listed in this leaflet. See section 4.

Throughout this leaflet, Onkotrone Injection 2mg/ml concentrate for solution for infusion will be called Onkotrone.

In this leaflet:

1 What Onkotrone is and what it is used for

Onkotrone contains the active substance mitoxantrone. Onkotrone 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. Mitoxantrone prevents cancer cells from growing, as a result of which they eventually die.

Onkotrone 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). Onkotrone 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.

2 What you need to know before you use Onkotrone

Do not use Onkotrone:
- 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").

Warning and precautions

Onkotrone 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).
Onkotrone should be given by slow and freely flowing infusion into the vein.
Onkotrone 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 Onkotrone leaks in surrounding tissue (extravasation) during administration.
Onkotrone 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 Onkotrone:
- if you have liver problems;
- if you have kidney problems;
- if you have use Onkotrone 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 Onkotrone;
- if you plan a vaccination or immunisation during treatment. Vaccinations and immunisations may not work during treatment with Onkotrone 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 Onkotrone.

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

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

Blood tests prior and during treatment with Onkotrone

Onkotrone may affect your blood cell counts. Before you start Onkotrone 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 Onkotrone in high doses (>14 mg/m² per day x 3 days).

Heart function tests prior and during treatment with Onkotrone

Onkotrone 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 Onkotrone 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 Onkotrone and at regular intervals during therapy.

Acute myeloid leukemia (AML) and Myelodysplastic syndrome

A group of anticancer medicines (topoisomerase II inhibitors), including Onkotrone, 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

Onkotrone may cause a blue-green colouration to the urine for 24 hours after administration. A bluish disolouration 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 Onkotrone

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 Onkotrone:
- 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 Onkotrone 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:
  - 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).

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 Onkotrone. 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 Onkotrone and you are prescribed a new medicine that you have not already taken at the same time as Onkotrone.
Vaccinations and immunisation (protection against the vaccination substances) may not work during treatment with Onkotrone 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

Onkotrone may cause damage to your unborn child. Therefore you should avoid becoming pregnant.

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

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 Onkotrone.

Breast-feeding

Onkotrone 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

Onkotrone 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

Onkotrone 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.

Turn over leaflet for further information.

The following information is intended for healthcare professionals only:

Onkotrone Injection

Technical Information

This technical leaflet does not include all the information about the product. Refer to the Summary of Product Characteristics before use.

Posology

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/m² from prior dose, after recovery.
If WBC nadir < 1,000 µl or platelet nadir < 25,000 µl	Any duration	Decrease by 4 mg/m² 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.

3 How to use Onkotrone

Posology and method of administration

Onkotrone 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 Onkotrone, especially with the skin, mucous membranes (moist body surfaces, such as the lining of the mouth) and eyes. The individual dose of Onkotrone is calculated by your doctor. The recommended dose is based on your body surface area, which is calculated in square metres (m^2) 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 Onkotrone is used alone:

The recommended initial dosage of Onkotrone 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)

Onkotrone has been given as part of combination therapy.

In metastatic breast cancer, combinations of Onkotrone with other cytotoxic agents including cyclophosphamide and 5-fluorouracil or methotrexate and mitomycin C have been shown to be effective.

Onkotrone 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 Onkotrone is used in combination chemotherapy, the initial dose of Onkotrone should be reduced by 2-4 mg/m² below the doses recommended when Onkotrone 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 Onkotrone 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 Onkotrone 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).

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.

Other side effects may include:

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 chemotherpy or radiotherapy.
- Insufficient production of bloods 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 (myelodisplastic 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 ventrical 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 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):
  - Reddening (erythema).
  - Swelling.
  - Pain.
  - Burning feeling and/or discolouration of the skin.
  - 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).

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Onkotrone

- 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 after EXP. The expiry date refers to the last day of that month.
- Do not store above 25ºC.
- Do not freeze.
- Diluted solutions can be stored as above for 8 hours.

Medicines should not be disposed of via wastewater or household waste. If you have any medicine left over, take it back to your pharmacist.

6 Contents of the pack and other information

What Onkotrone contains

The active substance is mitoxantrone hydrochloride. The strength of Onkotrone is 2 mg mitoxantrone/ml. Each vial contains 20 mg, 25 mg or 30 mg mitoxantrone depending on the size of the vial.

The other ingredients are sodium chloride, sodium acetate, acetic acid, sterile water (called 'water for injections').

What Onkotrone looks like and contents of the pack

Onkotrone is a dark blue solution in clear glass vials.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation holder is:
Baxter Healthcare Ltd
Caxton Way, Thetford, Norfolk, IP24 3SE, UK
Send all enquiries to this address.

Onkotrone is manufactured by:
Baxter Oncology GmbH
Kantstrasse 2, 33790 Halle/Westfalen, Germany

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Is this leaflet hard to see or read?
Telephone 01635 206345 for an audio-tape, large print leaflet or other formats.

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.

Mode of administration

Onkotrone concentrate should be given by intravenous infusion only.

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

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

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

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