SCHEDULING STATUS S4

MITOXANTRONE-HEXAL 20 mg/10 mℓ (solution for infusion)

Mitoxantrone hydrochloride

Sugar free

Read all of this leaflet carefully before you are given MITOXANTRONE-HEXAL.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- MITOXANTRONE-HEXAL has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

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

1. What MITOXANTRONE-HEXAL is and what it is used for

Mitoxantrone hydrochloride, which is the active ingredient of MITOXANTRONE-HEXAL, is an antineoplastic or anti-cancer medicine and belongs to the subgroup of anti-cancer medicines called anthracyclines. MITOXANTRONE-HEXAL prevents cancer cells from growing.

MITOXANTRONE-HEXAL is used in the treatment of:

- Breast cancer, including the advanced stage (metastatic form) of breast cancer.
- A certain form of lymph node cancer (non-Hodgkin's lymphoma).
- Acute non-lymphocytic leukaemia in adults. Leukaemia is a type of cancer of the blood in which the bone marrow makes too many white blood cells.
- MITOXANTRONE-HEXAL is used in combination with low doses of corticosteroids to treat advanced severely painful prostate cancer that is not sensitive to hormone treatment and that is at an advanced stage.

2. What you need to know before you receive MITOXANTRONE-HEXAL

MITOXANTRONE-HEXAL should not be administered to you:

- If you are hypersensitive (allergic) to mitoxantrone hydrochloride or any of the ingredients of MITOXANTRONE-HEXAL, including sulphites that may be produced during the manufacturing of MITOXANTRONE-HEXAL.
- If you are pregnant or breastfeeding.

Warnings and precautions

MITOXANTRONE-HEXAL 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).

MITOXANTRONE-HEXAL should be given by slow and freely flowing infusion into the vein.

MITOXANTRONE-HEXAL 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 MITOXANTRONE-HEXAL leaks in surrounding tissue (extravasation) during administration.

MITOXANTRONE-HEXAL 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.

Special care should be taken with MITOXANTRONE-HEXAL:

- If your bone marrow is not working well (is depressed) or if you are in generally poor health. While you are receiving MITOXANTRONE-HEXAL, your doctor will frequently carry out blood tests, particularly to monitor the number of white blood cells in your blood.
- If you have ever had a heart abnormality or symptoms of heart failure, undergone radiotherapy of the chest, or had previous therapy with other anti-cancer medicines (including MITOXANTRONE-HEXAL, anthracyclines or anthracenediones, such as daunorubicin or doxorubicin). In these cases, it is to be expected that you will develop heart problems. Your doctor will frequently monitor your heart function to determine whether your heart is working properly.
- If you are using other cardiotoxic medicines. Concomitant use with MITOXANTRONE-HEXAL may increase the risk for cardiotoxicity.
- If you have an infection. This should be treated before the treatment with MITOXANTRONE-HEXAL is started.
- If you plan a vaccination or immunisation during treatment. Vaccinations and immunisations may not work during treatment with MITOXANTRONE-HEXAL and for 3 months after the end of treatment.
- If you and your partner are trying to become pregnant.
- If you suffer from severe kidney or liver insufficiency.

Your doctor will frequently monitor your liver function, your heart function and will perform tests on your blood.

Blood tests prior and during treatment with MITOXANTRONE-HEXAL

MITOXANTRONE-HEXAL may affect your blood cell counts. Before you start MITOXANTRONE-HEXAL 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 1500 cells/mm^3).
- If you use MITOXANTRONE-HEXAL in high doses (>14 mg/m^2 per day x 3 days).

Heart function tests prior and during treatment with MITOXANTRONE-HEXAL

MITOXANTRONE-HEXAL 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 MITOXANTRONE-HEXAL 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 MITOXANTRONE-HEXAL and at regular intervals during therapy. If you receive MITOXANTRONE-HEXAL 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 leukaemia (AML) and myelodysplastic syndrome

A group of anticancer medicines (topoisomerase II inhibitors), including MITOXANTRONE-HEXAL, 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).

You should also be aware that MITOXANTRONE-HEXAL can cause discolouration of:

- Your urine (your urine can be stained blue-green for up to a day after treatment).
- Your skin and nails (these can be stained blue).
- The whites of your eyes (these can be stained blue).

All these discolourations are transient and can last a few days.

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 MITOXANTRONE-HEXAL 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

MITOXANTRONE-HEXAL 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 with MITOXANTRONE-HEXAL. Do not give MITOXANTRONE-HEXAL 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 MITOXANTRONE-HEXAL

Always tell your healthcare professional if you are taking any other medicine (this includes complementary or traditional medicines).

Tell your doctor if you are using any of the following medicines

- Other bone marrow suppressant medicines which reduce the activity of the bone marrow (myelosuppressive, e.g. anti-cancer medicines). These can do more damage to your bone marrow if they are used together with MITOXANTRONE-HEXAL. These can also increase the damage MITOXANTRONE-HEXAL does to your bone marrow.
- Medicines that supress your immune system (immunosuppressive agents).
- Products which can damage the heart (e.g. anthracyclines) since the damage these medicines cause to your heart can be increased.
- Topoisomerase II inhibitors (a group of anti-cancer medicines, including MITOXANTRONE-HEXAL) in combination with other anti-cancer medicines and/or radiotherapy against cancer. This can lead to:
  - A cancer of the white blood cells (acute myeloid leukaemia).
  - A bone marrow abnormality which causes abnormally formed blood cells which can develop into leukaemia (myelodysplastic syndrome, MDS).
- Antivitamin K, in particular if you are receiving MITOXANTRONE-HEXAL because you have cancer.
- Vaccinations, Immunisation (protection against the vaccination substances) may not work during treatment with MITOXANTRONE-HEXAL.

MITOXANTRONE-HEXAL with food and drink

Not applicable.

Pregnancy, breastfeeding and fertility

Pregnancy

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other health care professional for advice before receiving MITOXANTRONE-HEXAL.

MITOXANTRONE-HEXAL may damage your unborn child. You should therefore not receive MITOXANTRONE-HEXAL if you are pregnant.

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

You should avoid becoming pregnant. If you or your partner is being treated with MITOXANTRONE-HEXAL, you must use an effective method of contraception. 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 MITOXANTRONE-HEXAL.

Breastfeeding

If you are breastfeeding, you must stop breastfeeding before the treatment is started, during treatment and for up to one month after the last administration. MITOXANTRONE-HEXAL can reach your baby via breast milk and may cause serious adverse reactions in your baby.

Fertility

MITOXANTRONE-HEXAL 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. Sperm preservation should be considered in male patients.

Driving and using machines

Because of its possible side effects, MITOXANTRONE-HEXAL can influence your ability to drive and use machines. If you suffer from these side effects, do not drive any vehicles and/or use any machines.

3. How to receive MITOXANTRONE-HEXAL

Do not share medicines prescribed for you with any other person.

You will not be expected to give yourself MITOXANTRONE-HEXAL. It will be given to you by a person who is qualified to do so.

Your doctor will determine the correct dosage for your condition.

Your doctor will tell you how long your treatment with MITOXANTRONE-HEXAL will last. If you have the impression that the effect of MITOXANTRONE-HEXAL is too strong or too weak, tell your doctor or pharmacist.

If you receive more MITOXANTRONE-HEXAL than you should

Since a healthcare professional will administer this medicine, he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

If you missed a dose of MITOXANTRONE-HEXAL

You should not receive a double dose to make up for the forgotten individual doses.

4. Possible side effects

MITOXANTRONE-HEXAL can have side effects.

Not all side effects reported for MITOXANTRONE-HEXAL are included in this leaflet. Should your general health worsen or if you experience any untoward effects while receiving MITOXANTRONE-HEXAL, please consult your doctor, pharmacist or other healthcare professional for advice.

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

- Reduction in red blood cells, which can make the skin pale and cause weakness or breathlessness.
- Bruising, unusual bleeding, such as coughing up blood, blood in your vomit or urine, or black stools (platelet reduction).
- 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).
- Abnormal heart beats.
- Severe life-threatening allergic reaction – you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth, skin, tongue or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint.
- Fever or infections.

Frequent side effects:

- Hypersensitivity reactions.
- Fever.
- Life threatening infections.
- Myelosuppression (reduced activity of the bone marrow).
- Leukopenia: a low number of leukocytes (white blood cells) as determined by blood tests.
- Anaemia (if the body has a shortage of red blood cells) as determined by blood tests.
- Low number of a special type of white blood cells (neutropenia).
- Non-specific neurological side effects such as dizziness, neuritis (infection of the nerves), convulsion (seizures).
- Myocardial infarction (heart attack).
- Heart failure (congestive heart failure).
- Change in the ECG.

- Dysrhythmia (heart rhythm disturbances).
- The volume of blood that the left ventricle can pump is reduced, but there are no symptoms.
- Dyspnoea (shortness of breath).
- Nausea (feeling sick) and vomiting.
- Stomatitis (inflammation of the inside of the mouth).
- Diarrhoea.
- Constipation.
- Anorexia.
- Liver dysfunction.
- Alopecia (hair loss).
- Absence of menstruation.
- Reduction of spermiogenesis.
- Fatigue.
- Weakness.
- Discolouration of the urine.
- Transient blue staining of the whites of the eyes.

Less frequent side effects:

- Thrombocytopenia (a low number of platelets – a blood cell involved in the clotting of the blood) determined by blood tests.
- Allergic (anaphylactic/anaphylactoid) reactions including eczema (skin rash or itching), dyspnoea (shortness of breath), hypotension (low blood pressure).
- Suppression of immune system.
- Cardiomyopathy (weakening or change in the structure of the heart muscle).
- Opportunistic infections.
- Infections of the upper airways.
- Pneumonia (lung inflammation).

- Infections of the urinary tract.
- Sepsis (blood poisoning).
- Acute leukaemia (cancer of the white blood cells).
- Acute myeloid leukaemia (AML, cancer of the white blood cells).
- Myelodysplastic syndrome (MDS), a bone marrow abnormality which causes the formation of abnormal blood cells which leads to leukaemia. AML and MDS can be caused by topoisomerase II inhibitors if these are used with other anti-cancer medicines and/or radiotherapy. Topoisomerase II inhibitors are a group of anti-cancer medicines to which mitoxantrone belongs.
- Bone marrow failure (abnormal reduction in the number of blood cells in an organ or in tissue).
- Low number of a special type of white blood cells (granulocytopenia).
- Abnormal white blood cell count (leukocytes).
- Bruising, bleeding.
- Heart problems which can cause shortness of breath or swelling of the ankles.
- Chest pain.
- Sinus bradycardia (slowed heartbeat).
- Arrhythmia (irregular heart beat).
- Phlebitis (local vein infection).
- Gastrointestinal bleeding.
- Mucositis (inflamed mucous membranes).
- Abdominal pain.
- Changed sense of taste.
- Loss of appetite.
- Changes in weight.
- Blue staining of the skin and nails.

- Nail abnormalities (e.g. detachment of the nail from the nail bed, changes in nail texture and structure).
- Tumour lysis syndrome. This causes hyperuricemia, hyperkalaemia and hyperphosphatemia (elevated concentrations of uric acid, potassium, phosphate and reduced concentration of calcium in the blood).
- Anxiety.
- Confusion.
- Drowsiness.
- Paraesthesia (tingling sensation).
- Headache.
- Conjunctivitis (inflammation of the mucous membranes in the eye and the eyelids).
- Hepatotoxicity (liver damage).
- Elevated liver enzyme concentrations (in blood tests).
- Extravasation (leakage of medicines form the vein into the surrounding tissue which can lead to erythema (reddening), swelling, pain, burning feeling and/or discolouration of the skin.
- Oedema (swelling).
- Erythema (skin inflammations).
- Tissue necrosis.
- Red rash.
- Skin discolouration.
- Hyperuricaemia (elevated concentration of uric acid in the blood).
- Changes in chemical values in the blood (elevated creatinine and nitrogen concentration in the blood).
- Increased urea concentration in the blood.

If you have leukaemia, you will have more frequent and severe side effects. In particular inflammation of the oral mucosa (inflammation of the inside of the mouth) and mucositis (inflammation of the mucous membranes) can occur.

Reporting of side effects

If you notice any side effects not mentioned in this leaflet, please inform your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of MITOXANTRONE-HEXAL.

Suspected side effects can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

5. How to store MITOXANTRONE-HEXAL

Store at or below 25 °C. Do not freeze.

Following admixture, unused portions of MITOXANTRONE-HEXAL should be discarded after 24 hours.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What MITOXANTRONE-HEXAL contains

The active substance is mitoxantrone hydrochloride. Each MITOXANTRONE-HEXAL solution for infusion contains 2,328 mg of mitoxantrone hydrochloride per 1 mℓ of solution.

Inactive ingredients in the tablet are

The other ingredients are glacial acetic acid, hydrochloric acid (for pH adjustment), sodium acetate, sodium chloride, anhydrous sodium sulphate and water for injection.

What MITOXANTRONE-HEXAL looks like and contents of the pack

MITOXANTRONE-HEXAL is a clear, blue solution, free of particles.

10 mℓ colourless glass vials (type I) closed with fluoropolymer-coated halobutyl rubber stoppers and sealed with aluminium crimp caps.

Holder of Certificate of Registration

Sandoz SA (Pty) Ltd[1]

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2090

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Access to the corresponding Professional Information

Not applicable.

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