PACKAGE LEAFLET: INFORMATION FOR THE USER

Doxorubicin 2 mg/ml

Concentrate for solution for infusion

doxorubicin hydrochloride

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 nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. WHAT DOXORUBICIN IS AND WHAT IT IS USED FOR

Doxorubicin belongs to a group of antitumour (anti-cancer) medicines called anthracyclines. Doxorubicin damages the tumour (cancer) cells and ensures that they can no longer grow.

Doxorubicin is used to treat the following types of cancer:
- lung cancer (small cell lung cancer)
- certain bladder cancers (locally advanced or spreading stage). It is also used intravesically (in the bladder) in early (superficial) bladder cancer to prevent recurrence of bladder cancer after surgery
- bone cancer (osteosarcoma) given before surgery and given following surgery
- breast cancer
- certain cancers of the blood (acute lymphatic or myeloblastic leukaemias)
- cancer of the lymphatic tissue (Hodgkin's and non-Hodgkin's lymphoma)
- cancer of the bone marrow (multiple myeloma)
- cancers of the thyroid (advanced papillary/follicular thyroid cancer, anaplastic thyroid cancer)
- cancer found in the soft tissue (advanced soft tissue sarcoma in adults)
- recurrent cancer of the ovaries
- cancer of the lining of the uterus (advanced or recurrent endometrial cancer)
- a certain childhood kidney cancer (Wilm´s tumour)
- childhood cancer of the nervous tissue (advanced neuroblastoma).

Doxorubicin is also used in combination with other anti-cancer drugs.

As Doxorubicin is an anti-cancer medicine it will be administered to you in a special unit and under the supervision of a doctor qualified in the use of anti-cancer medicines. The unit's personnel will explain to you what you need to take special care of during and after the treatment. This leaflet may help you to remember that.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE DOXORUBICIN

Do not use Doxorubicin:
- if you are allergic to doxorubicin or any of the other ingredients of this medicine (listed in section 6) or to other anthracyclines.
- if you have been told that your blood is thin (your bone marrow is not working well).
- if you have, or ever have had, any heart problems.
- if you have received doxorubicin, other anthracyclines, other anti-tumour medicines or immunosuppressive medicines before.
- if you tend to bleed easily.
- if you suffer from any kind of infection.
- if you suffer from mouth ulcers.
- if your liver is not working well.
- if you suffer from an infection of the bladder or if you have blood in your urine (in case the medicine is given to you by an administration into your bladder)
- if you are breast-feeding.

Warnings and precautions

Talk to your doctor or nurse before using Doxorubicin:
- if you have had any radiotherapy before,
- if you are pregnant, trying to become pregnant, likely to want to try to become pregnant in the future or if you want to father a child,
- if you are on a controlled sodium diet.

If there is a burning sensation in the area of the infusion, this can be a sign of an injection error and the infusion must be stopped immediately.

You should avoid contact to persons recently vaccinated against polio when you are under treatment with Doxorubicin.

Other medicines and Doxorubicin

Tell your doctor if you are taking, have recently taken or might take any other medicines.

The following medications can interact with Doxorubicin:
- Other cytostatics (medication against cancer) e.g. anthracyclines (daunorubicin, epirubicin, idarubicin), cisplatin, cyclophosphamide, cyclosporin, cytarabine, dacarbazine, dactinomycin, fluorouracil, mitomycin C, taxanes (e.g. paclitaxel), mercaptopurine, methotrexate, streptozocin
- Cardioactive medicines (medications for heart diseases), e.g. calcium channel blockers, verapamil, digoxin
- Inhibitors of cytochrome P-450 (medicines that stop the substance cytochrome P-450, which is important for the detoxification of your body, from working; e.g. cimetidine)
- Medicine inducing cytochrome P-450 (e.g. rifampicin, barbiturates)
- Antiepileptic medicines (e.g. carbamazepine, phenytoin, valproate)
- Heparin (prevents the clotting of the blood)
- Amidopyrine derivatives (pain-killers)
- Antiretroviral medicines (medications against special forms of viruses, e.g. ritonavir against AIDS)
- Chloramphenicol
- Sulphonamides (medications against bacteria)
- Progesterone (e.g. at threatening miscarriage)
- Amphotericin (used to treat fungal infections)
- Live vaccines (e.g. against polio myelitis, malaria)
- Trastuzumab (used in the treatment of breast cancer)
- Clozapine (antipsychotic medicine)
- Dose adjustment of uric acid lowering agents may be necessary

Please note that these statements may also apply to products used some time ago or at some time in the future.

Pregnancy and breast-feeding and fertility

If you are a woman, you should not get pregnant during treatment with doxorubicin or up to 6 months after treatment.
If you are a man, you should take adequate precautions to ensure that your partner does not become pregnant during your treatment with doxorubicin or up to 6 months after treatment. If you are considering becoming parents after the treatment please discuss with your doctor.

Because doxorubicin may cause permanent infertility, it is advised to discuss with your doctor the possibility of freezing sperm before treatment start (cryo-preservation or cryo-conservation).

Doxorubicin is not recommended if you are pregnant.

Breast-feeding must be discontinued for the duration of Doxorubicin therapy.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Due to the frequent occurrence of drowsiness, nausea and vomiting, you are not advised to drive cars and operate machinery.

Doxorubicin contains sodium

5 ml vial: This medicine contains 17.7 mg sodium (< 1 mmol) per 5 ml vial of concentrate, that is to say essentially 'sodium-free'.

25 ml vial: This medicine contains 88.5 mg sodium (main component of cooking/table salt) in each 25 ml vial of concentrate. This is equivalent to 4.4% of the recommended maximum daily dietary intake of sodium for an adult.

3. HOW TO USE DOXORUBICIN

Method and routes of administration

Do not administer the medicine yourself. Your medicine will be given to you as part of an intravenous infusion, into a blood vessel, under the direction of specialists.
You will be monitored regularly both during and after your treatment.
If you suffer from superficial bladder cancer it is possible that you may receive your medicine into your bladder (intravesical use).

Dosage

The dosage is usually calculated on the basis of your body surface area. 60 – 75 mg per square metre of body surface area may be given every three weeks when used alone. The dosage may need to be reduced to 30 – 40 mg per square metre of body surface area when given in combination with other anti-tumour medicines.
The dosage may be given as either a single dose every three weeks or divided over three consecutive days (20 – 25 mg per square metre of body surface area on each day). If given weekly the recommended dose is 20 mg per square metre of body surface area. Your doctor will advise you of how much you will need.

Patients with reduced liver or kidney function

If your liver or kidney function is reduced, the dosage should be decreased. Your doctor will advise you of how much you need.

Use in children/obese patients/elderly/patients after radiotherapy

The dosage may need to be reduced in children, in obese patients and the elderly or if you have received any radiotherapy. Your doctor will advise you of how much you need.

If you use more Doxorubicin than you should

During and after treatment you will be carefully monitored by your doctor or nurse. The symptoms of an overdose are an extension of doxorubicin's possible side effects, particularly the blood changes and heart problems. Heart disorders may even occur up to six months after you received the overdose.
In case of an overdose your doctor will take appropriate measures, such as a blood transfusion and/or treatment with antibiotics.

Please tell your doctor if any of the symptoms occur.

Effects when treatment with Doxorubicin is interrupted or stopped early

Your doctor will decide on the duration of your treatment with Doxorubicin. If the treatment is stopped before the advised course of treatment is finished, the effects of the doxorubicin therapy might be reduced.
Ask your doctor for advice if you wish to stop the treatment.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor straight away if you notice any of the following serious side effects:

They have been ranked according to their potential seriousness.
- You may develop hives, fever, chills, severe hypersensitivity. This type of allergic reaction can be life-threatening.
- Heart problems – for example you may notice your heart beating abnormally quickly, with an increase in pulse rate. In case of heart problems, routine ECG monitoring is commonly applied. If you have suffered from heart problems (even a long time ago) before treatment with Doxorubicin make sure to tell your doctor about this.
- Blood changes – e.g. your vulnerability for infections may increase, you may suffer from unusual bleedings and you may observe signs of anaemia (weakness, tiredness, laboured breathing with a feeling of apprehension).

Your urine may be coloured red, particularly the first time that you pass urine after each injection of Doxorubicin. This is nothing to worry about and your urine will soon return to its normal colour.

Common (may affect up to 1 in 10 people):
- decreased activity in bone marrow leads to reduced blood cells
- cardiomyopathy (heart disease in which your heart muscle does not work properly)
- ECG changes (includes irregular heartbeat)
- deficiency in blood cells causing infection
- nausea and/or vomiting (feeling and /or being sick)
- mucositis (inflammation of membranes in digestive tract, starts with burning sensations in mouth or pharynx)
- anorexia (eating disorder)
- diarrhoea – may result in dehydration
- bladder inflammation sometimes with painful urination, need to urinate more often or during night or blood in urine (following administration into the bladder)
- alopecia (hair loss)
- sepsis (serious infection of the whole body)
- septicaemia (bacterial infection of the blood)

Uncommon (may affect up to 1 in 100 people):
- dehydration
- phlebitis (vein inflammation)
- local hypersensitivity reaction of the field of radiation
- bleeding in stomach or bowel
- abdominal pain
- ulceration and necrosis (death of cells of the tissue) of the digestive tract
- inflammation of voice box and throat

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doxorubicin hydrochloride

The following information is intended for healthcare professionals only:

Shelf life

Unopened vials: 2 years.
Opened vials: The product should be used immediately after opening the vial.

Prepared infusion solutions:
Chemical and physical in-use stability has been demonstrated in 0.9% sodium chloride injection and 5% dextrose injection for up to 7 days at 2 – 8°C and 25°C when prepared in glass containers protected from light.

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 and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic condition.

Incompatibilities

Doxorubicin must not be mixed with heparin, as this will result in precipitation. Until detailed compatibility information about miscibility is available, Doxorubicin should not be mixed with other medicinal products other than 0.9% sodium chloride injection and 5% dextrose injection.

Incompatibilities with the following products have been reported:
Aminophyllin, cephalotin, dexamethasone, fluorouracil, hydrocortisone.

Prolonged contact with any solution of an alkaline pH should be avoided, as it will result in hydrolysis of the medicinal product.

Special precautions for disposal and other handling

For single use only.

Doxorubicin is a potent cytotoxic agent which should only be prescribed, prepared and administered by professionals who have been trained in the safe use of the preparation. The following guidelines should be followed when handling, preparing and disposing of doxorubicin.

Preparation

1. Personnel should be trained in good technique for handling.
2. Pregnant staff should be excluded from working with this drug.
3. Personnel handling doxorubicin should wear protective clothing: goggles, gowns, disposable gloves and masks.
4. All items used for administration or cleaning, including gloves, should be placed in high risk waste disposal bags for high temperature (700°C) incineration.
5. All cleaning materials should be disposed of as indicated previously.
6. Always wash hands after removing gloves.

Contamination

1. In case of contact with skin or mucous membrane, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not graze the skin by using a scrubbing brush. A bland cream may be used to treat transient stinging of skin.
2. In case of contact with eye(s), hold back the eyelid(s) and flush the affected eyes with copious amounts of water for at least 15 minutes or normal sodium chloride 9 mg/ml (0.9%) solution for injection. Then seek medical evaluation by a physician or eye specialist.
3. In the event of spillage or leakage treat with 1% sodium hypochlorite solution or most simply with phosphate buffer (pH>8) until solution is destained. Use a cloth/sponge kept in the designate area. Rinse twice with water. Put all cloths into a plastic bag and seal for incineration.

Rare (may affect up to 1 in 1,000 people):
- secondary leukaemia (blood cancer arisen from combined treatment with a special kind of other anti-cancer medicines)
- tumour lysis syndrome (complications of having chemotherapy)
- severe allergic reactions including skin rash, itching, fever, chills and breathing difficulties
- abnormal reduction of white blood cells when given with other cancer medicines
- conjunctivitis (usually causing red watery eyes)
- hives
- rash
- erythematous reactions (rash-like symptoms) along the vein used for the injection
- skin and nails may appear darker than usual.
- separation of nail plates
- shivering
- fever
- dizziness

Not known (cannot be estimated from the available data):
- severe reducing in blood cells may cause spontaneous bleeding or anaemia
- hot flushes
- severe heart failure (loss of cardiac function)
- inflammation of the veins
- clot formation in a blood vessel
- irregular heart beat
- bronchospasm (coughing or difficulty in breathing)
- inflammation of the lung after radiation
- increase of liver enzymes
- hand-foot syndrome
- local death of cells of tissue
- loss of renal function may lead to renal failure
- high uric acid level in blood
- absence of menstruation
- infertility in men, low sperm volume or lack of sperm

Burning, redness and swelling at the administration site may occur. If this is the case during an infusion you should inform the doctor or nurse, because the injection should be stopped immediately and restarted at another site.

Reporting of side effects
If you get any side effects, talk to your doctor, 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 DOXORUBICIN

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 carton and vial after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2- 8°C). Keep the vial in the outer carton in order to protect from light.

Do not use this medicine if you notice the solution is not clear, red and free of particles.

Any unused product or waste material should be disposed of in accordance with local requirements. Observe guidelines for handling cytotoxic drugs.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Doxorubicin contains
- The active substance is doxorubicin hydrochloride.
- The other ingredients are sodium chloride, hydrochloric acid (for pH adjustment) and water for injections.

Each ml contains 2 mg doxorubicin hydrochloride.
Each 5 ml vial contains 10 mg of doxorubicin hydrochloride.
Each 25 ml vial contains 50 mg of doxorubicin hydrochloride.

What Doxorubicin looks like and contents of the pack
Doxorubicin 2 mg/ml concentrate for solution for injection is a clear red solution.
Doxorubicin is packed in amber glass vial with rubber stopper and sealed with flip-off aluminium cap.

Pack sizes:
1 x 5 ml
1 x 25 ml

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Hikma Farmacêutica (Portugal) S.A.
Estrada do Rio da Mó, nº8, 8A, 8B
Fervença
2705-906 Terrugem SNT
Portugal

Manufacturer
Thymoorgan Pharmazie GmbH
Schiffgraben 23
38690 Vienenburg
Germany

Distributor
Consilient Health Limited
No1 Church Road
Richmond upon Thames
Surrey, TW9 2QE
UK

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Consilient Health

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Intravenous administration:
The solution is given via the tubing of a freely running intravenous infusion of sodium chloride 0.9 % or dextrose 5 % into a large vein using a Butterfly needle, taking 2 to 3 minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation, which can lead to severe local cellulitis and necrosis.

Intravesical administration:
Doxorubicin can be given by intravesical instillation for treatment of superficial cancer of the bladder and to prevent relapse after transurethral resection (T.U.R).
The recommended dose for intravesical treatment of superficial cancer of the bladder is 30-50 mg in 25-50 ml of physiological saline per instillation. The optimal concentration is about 1 mg/ml. The solution should remain in the bladder for 1-2 hours. During this period the patient should be turned 90° every 15 minutes. To avoid undesired dilution with urine the patient should be informed not to drink anything for a period of 12 hours before the instillation (this should reduce the production of urine to about 50 ml/h). The instillation may be repeated with an interval of 1 week to 1 month, dependent on whether the treatment is therapeutic or prophylactic.

Doxorubicin should not be administered by the intramuscular, subcutaneous, oral or intrathecal route.

Disposal
Single use only. Any unused medicinal product or waste materials that have been used for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents with due regard to current laws related to the disposal of hazardous waste. Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.