Package leaflet: Information for the user

Doxorubicin 2mg/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 pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- The full name of this medicine is Doxorubicin 2mg/ml Concentrate for Solution for Infusion but within the leaflet it will be referred to as Doxorubicin.

What is in this leaflet:

1 What Doxorubicin is and what it is used for

Doxorubicin belongs to a group of anti-cancer medicines called anthracyclines. Doxorubicin is used to treat the following types of cancer:
- Small cell lung cancer
- Bladder cancer
- Bone cancer
- Breast cancer
- Cancer of the blood
- Cancer in the lymph system (Hodgkin and Non-Hodgkin's lymphoma)
- Cancer of the bone marrow
- Cancer in the thyroid gland
- Cancer in soft tissue (in adult age)
- Recurrent cancer in the ovaries or in the mucous membrane lining the uterus
- Certain type of kidney cancer that affects children (Wilm´s tumour)
- Certain type of advanced cancer in nerve cells that affects children (neuroblastoma).

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

2 What you need to know before receiving Doxorubicin

Do not receive Doxorubicin
- if you are **allergic to doxorubicin** or any of the **other ingredients** of this medicine (listed in section 6)
- if you are **allergic** to drugs of the class **anthracyclines** or **anthracendiones**
- if you are **breastfeeding**.

Please talk to your doctor in case any of the above applies to you.

You must not receive Doxorubicin intravenously
- if you have been told after previous cancer therapy that you had persistent **decrease in the production of blood cells** (your bone marrow was not working well)
- if you had after previous cancer therapy **severe inflammation or ulcers in the mouth**
- if you have some **heart problems**
- if you tend to **bleed easily**
- if you suffer from any kind of **general infections**
- if your **liver** is not working well
- if you have previously received doxorubicin or other anthracyclines up to the **maximal cumulative dose.**

Please talk to your doctor in case any of the above applies to you.

You must not receive Doxorubicin in the bladder
- if you have a **tumour** that has grown into the bladder wall
- if you have **urinary tract infection**
- if you have **inflammation of the bladder**
- if you have **blood in the urine**
- if you have problems with the **instillation** (e.g. urethral obstructions).

Please talk to your doctor in case any of the above applies to you.

Warnings and precautions
Talk to your doctor before receiving Doxorubicin
- if you **are or might be pregnant**, see also section on pregnancy and breastfeeding below
- if you have had any **radiotherapy** before
- if you are 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 have **kidney** problems
- if you have or ever have had any **heart** problems.

Doxorubicin strongly reduces blood cell production in the bone marrow. This may make you more prone to infections or bleeding. Tell your doctor in case of fever or other sign of infection or in case of bleeding.

Vaccination is not recommended. Contact to persons recently vaccinated against polio should be avoided.

Doxorubicin should be administered only under the supervision of a qualified physician experienced in cancer therapy. Also, patients must be carefully and frequently monitored e.g. blood status and function test of the heart, liver and kidney.

If you feel a stinging or burning sensation in the area of the infusion tell your doctor or other health care personnel immediately. Such a pain can occur if the medicine leaks out of the vein and then you will need an appropriate therapy.

Other medicines and Doxorubicin
Tell your doctor if you are taking, have recently taken or might take any other medicines. This is especially important in case of:
- other medication against cancer e.g. anthracyclines (daunorubicin, epirubicin, idarubicin, trastuzumab), cyclophosphamide, cytarabine, cisplatin, fluorouracil, taxanes (e.g. paclitaxel), mercaptopurine, methotrexate, streptozocin
- ciclosporin (used in organ and tissue transplants)
- medications for heart diseases (cardioactive drugs) e.g. calcium channel blockers and digoxin
- medicines that lower uric acid level in your blood
- rifampicin (antibiotic)
- cimetidine (used in the treatment of heartburn and stomach ulcers)
- live vaccines (e.g. polio (myelitis))
- phenytoin, carbamazepine, valproate, phenobarbital and other barbiturate (used in the treatment of epilepsy)
- chloramphenicol and sulfonamides (medicines for infections)
- amphotericin B (medication for fungal infections)
- medicines for viral infections, such as ritonavir (used to treat HIV)
- clozapine (an antipsychotic)
- amidopyrine derivates (for pain and inflammation).

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 using this medicine.

It is known that doxorubicin passes the placenta and harms the unborn in animal experiments. Therefore you should not receive doxorubicin if you are pregnant. Tell your doctor immediately if you are pregnant or think you are pregnant.

Women should not get pregnant during the treatment with Doxorubicin or up to 6 months after treatment. Men should take adequate precautions to ensure that their partner does not become pregnant during the treatment with doxorubicin and up to 6 months after the treatment. Sexually active men and women should therefore use effective contraceptive method during and up to 6 months after treatment.

Men should also seek advice on cryo-conservation (or cryo-preservation) of sperm prior to treatment because of the possibility
of irreversible infertility due to therapy with doxorubicin. If you are considering becoming parents after the treatment please discuss this with your doctor.
The drug passes into human breast milk. Do not breast-feed while you are treated with Doxorubicin.

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

Doxorubicin contains sodium
This medicinal product contains 3.54mg (<1mmol) sodium per ml concentrate. This should be taken into consideration by patients on a controlled sodium diet.

3 How Doxorubicin is administered

Doxorubicin should only be given under supervision of a doctor with experience in cancer therapy.

Method and routes of administration
Your medicine will be given to you by intravenous infusion, into a blood vessel, under the direction of a specialist. Do not administer the medicine yourself. 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.

This medicinal product should be diluted before use.

Intravenous administration
The dosage is usually calculated on the basis of the body surface area. Doxorubicin may be given e.g. once a week, every three weeks or even with longer intervals between. The dose and frequency also depends on other anti-cancer medicines used, in addition to the type of disease and your general health. Your doctor will decide about the dose you will receive.
Instillation in the bladder
The dosage is 30-50mg doxorubicin in 25-50ml of physiological saline. The solution should remain in the bladder for 1-2 hours. During this period you need to turn about 90° every 15 minutes.

You should **not drink anything for 12 hours before** instillation in the bladder, to avoid undesired dilution of the medicine with urine. The instillation may be repeated with an interval of 1 week to 1 month. Your doctor will advise you of how often you need it.

Use in children
The dosage should be reduced in children. Your doctor will advise you on how much you need.

If you use more Doxorubicin than you should
As a doctor will be giving you your medicine, it is unlikely that you will receive an overdose.
However, if you have concerns you should let your doctor or nurse know immediately.
Acute overdosing worsens side effects like sores in the mouth, decreases the number of white blood cells and platelets

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The following information is intended for medical or healthcare professionals only:

Doxorubicin 2mg/ml Concentrate for Solution for Infusion

Doxorubicin hydrochloride

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. For recommendation on posology and method of administration see section 4.2 of the SPC for this medicinal product. The following guidelines should be followed when handling, preparing and disposing of doxorubicin.

For single use only.

Preparation
1. Cytotoxic agents should be prepared for administration only by personnel who have been trained in the safe handling of such preparations. Refer to local cytotoxic guidelines before commencing.
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.

Do not use Doxorubicin 2mg/ml Concentrate for Solution for Infusion if the solution is not clear, red and free of particles.

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 eye(s) with copious amounts of water for at least 15 minutes or normal sodium chloride 9 mg/ml (0.9%) solution for injection. Seek medical evaluation by a physician or eye specialist.
3. In the event of spillage or leakage treat with 1% sodium hypochlorite solution or phosphate buffer (pH>8) until solution is decoloured. Use a cloth/sponge kept in the designated area. Rinse twice with water. Put all cloths into a plastic bag and seal for incineration.

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in the blood and can lead to heart problems. In case of overdose you should receive appropriate treatment as your doctor will decide. Heart disorders may occur up to six months after an overdose.

If you missed a dose of Doxorubicin
Your doctor will decide on the duration of your treatment with Doxorubicin. If the treatment is stopped before the advised courses 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.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4 Possible side effects

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

Please contact your doctor or nurse immediately in case:
- you feel **dizzy**, **feverish**, **short of breath** with a **tight chest or throat** or have an **itchy rash**. This may be a type of allergic reaction which can be very serious
- you feel **tired** and **lethargic**. This may be sign of anemia (a low red blood cell count)
- you have **fever** or other **symptoms of infection**. This may be sign of low white blood cell counts
- you **bruise** or **bleed** more easily. This may be sign of low platelet count in your blood.

Very common (may affect more than 1 in 10 people)
- feeling sick, being sick, abdominal pain, digestive disorders, diarrhoea
- inflammation of the mucous membranes e.g. in the mouth or esophagus
- hair loss (normally reversible), skin redness, sensitivity of skin to artificial or natural light (photosensitivity)
- red colouration of the urine, for one or two days after administration. This is normal and nothing to worry about
- bone-marrow suppression (deficiency in blood cells) including reduction in number of white blood cells (causing infection), blood platelets (causing bleeding and bruises) and red blood cells (anaemia; so the skin can be pale and weakness may occur, or shortness of breath)
- severe heart complications (cardiotoxicity), like damage to the heart muscle or fast, slow or irregular pulse. Effects can appear shortly after the treatment is started or be observed several years later
- fever.

Common (may affect up to 1 in 10 people)
- bacterial infection
- bacterial infection in the blood
- cardiac arrhythmias (irregular heart beat, rapid heart rate, decreased heart rate), reduced amount of blood pumped through the heart, deterioration of the function of the heart muscle (cardiomyopathy) that can be life threatening
- bleeding (haemorrhage)
- eating disorder (anorexia)
- local allergic reaction of the field of radiation
- itching
- difficult or painful urination, bladder inflammation following instillation in the bladder, sometimes with irritation in the bladder, blood in the urine, painful urination, more frequent urination or decreased urine.

Uncommon (may affect up to 1 in 100 people)
- acute blood cancer (certain types of leukaemia)
- inflammation of a vein
- bleeding in the stomach or intestines
- ulcers in the mucous membranes of the mouth, pharynx, esophagus, stomach and the intestines
- ulcers and possible death of cells/ tissues of the colon when Doxorubicin is given in combination with the medicinal product cytarabine
- dehydration.

Rare (may affect up to 1 in 1,000 people)
- inflammation of the outermost layer of the eye (conjunctivitis)
- hives; skin rash and redness
- darkened areas of skin and nails; loosening of the nails (onycholysis)
- severe allergic reactions with or without shock, including skin rash, itching, fever and chills (anaphylactic reactions)
- shivering
- dizziness
- secondary leukaemia (blood cancer developed after treatment for another cancer), when Doxorubicin is used in combination with other anticancer drugs which damage the DNA
- tumour lysis syndrome (complications of having chemotherapy due to break-down products of dying cancer cells which for example can affect the blood and kidneys)
- injection site reactions including redness, rash and pain, inflammation of the vein (phlebitis), thickening or hardening of the wall of the vein (flebosclerose)
- a stinging or burning sensation at the administration site in relation to the medicine leaking out of the vein. This can lead to death of local tissue cells and needs appropriate treatment, in some cases surgical measures.

Very rare (may affect up to 1 in 10,000 people)
- flushing of the face
- changes in the heart function (unspecified ECG changes), isolated cases of life-threatening irregular heart beat (arrhythmias), heart failure, inflammation of the pericardium / myocardium, loss of nerve impulses in the heart
- clot formation in a blood vessel
- discoloration (pigmentation) of the oral mucosa
- swelling and numbness of the hands and feet (acral erythema), blistering, tissue damage especially of the hands and feet, causing redness, swelling, blisters, tingling or burning sensation where leakage of the drug in the tissues occur (palmarplantar erythrodysesthesia syndrome)
- acute kidney failure
- abnormally high uric acid levels in the blood
- absence of menstrual period
- fertility problems in men (reduction or absence of active sperm).

Not known (frequency cannot be estimated from the available data)
- increased tear production
- coughing or difficulty in breathing because of sudden narrowing of airways
- lung inflammation
- liver toxicity, which sometimes can progress to permanent damage of liver tissue (cirrhosis)
- transient increase of liver enzymes
- fat, bald or crusty patches of skin (actinic keratosis)
- severe pain and swelling in the joints
- weakness
- radiation damage (on the skin, lungs, throat, esophagus, stomach and intestinal mucosa, heart) already healing, may reappear following administration of doxorubicin.

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

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace, IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Doxorubicin

Keep out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the vial and outer carton. 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.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Contents of the pack and other information

What Doxorubicin contains
- The active substance is doxorubicin hydrochloride. Each vial contains 2mg/ ml doxorubicin hydrochloride.
- The other ingredients are sodium chloride, hydrochloric acid and water for injections.

What Doxorubicin looks like and contents of the pack
Doxorubicin 2mg/ml Concentrate for Solution for Infusion is a clear red solution.
Doxorubicin is packed in colourless glass vial with rubber stopper and sealed with aluminium cap with polypropylene disk. The vial will be packed with or without a protective plastic overwrap.

Pack sizes:
1 x 5ml vial
10 x 5ml vials
1 x 10ml vial
10 x 10ml vials
1 x 25ml vial
1 x 50ml vial

Marketing Authorisation Holder
Actavis Group PTC ehf.
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Actavis, Barnstaple, EX32 8NS, UK
Actavis Ireland, Euro Hs, Little Island, Cork

In use stability
Opened vials: Chemical and physical in-use stability has been demonstrated for 28 days at 2-8°C. From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Prepared infusion solutions: Chemical and physical stability after dilution, when protected from light, has been demonstrated for up to:
- 7 days at 2-8°C and 2 days at 25°C in 0.9% sodium chloride solution (PE bottle) in the concentration 1.25 mg/ml.
- 24 hours at 2-8°C and 25°C in 5% glucose solution (PP bag), in the concentration 1.25 mg/ml.
- 2 days at 2-8°C and 7 days at 25°C in 0.9% sodium chloride solution (PE bottle), in the concentration 0.5 mg/ml.
- 24 hours at 2-8°C and 7 days at 25°C in 5% glucose solution (PP bag), in the concentration 0.5 mg/ml.

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.

Storage times of the opened vial and diluted infusion solution are not additive.

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

Note:
Posology of S-liposomal doxorubicin and (conventional) doxorubicin as in Doxorubicin 2mg/ml Concentrate for Solution for Infusion are different. The two formulations cannot be used interchangeably.

Incompatibilities
Doxorubicin should not be mixed with heparin, as a precipitate may form and it should not be mixed with 5-fluorouracil as degradation may occur. Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug.
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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