

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

What is in this leaflet

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

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
- Advanced or recurrent cancer 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 Agila is also used in combination with other anti-cancer drugs.

What you need to know before you receive Doxorubicin

You must 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 suffer from any kind of general infections;
- if you have serious liver problems;
- if you have some heart problems;
- if you have previously received doxorubicin or other anthracyclines up to the maximal cumulative dose;
- if you tend to bleed easily.

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 tumour that has grown into the bladder wall;
- if you have urinary tract infection;
- if you have inflammation of the bladder;
- if you have problems with the instillation (e.g. urethral obstructions);
- if you have blood in the urine.

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

Warnings and precautions

Take special care with Doxorubicin and tell your doctor before treatment

- if you are or might be pregnant, see also section on pregnancy and breastfeeding below.
- if you have had any radiotherapy before;
- if you have gastrointestinal symptoms (inflammation, ulceration or diarrhoea)
- 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;
- if you are having other anticancer therapies.

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 before and/or during treatment e.g. blood status and function test of the heart, liver and kidney and radiographs of the lungs and chest.

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

Please 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;
- cimetidine (used in the treatment of heartburn and stomach ulcers);
- live vaccines (e.g. polio (myelitis));
- phenytoin, 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 derivatives (for pain and inflammation).

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking 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. In women, doxorubicin can cause infertility and absence of menstrual periods during the treatment. After the therapy, ovulation and menstruation return, although premature menopause can occur.

If you are considering becoming parents after the treatment please discuss this with your doctor.

The drug passes into human breast milk. Do not breastfeed 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 3.54 mg (<1 mmol) sodium per ml concentrate.

This should be taken into consideration by patients on a controlled sodium diet.

2. 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 anticancer medicines used as single agent or in combination with other cytotoxic agents or as a part a multidisciplinary procedures that include combination of chemotherapy, surgical procedure and radiotherapy and hormonal treatment, 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 30-50 mg docorubicin in 25-50 ml 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.

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 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 you doctor for advise if you wish to stop the treatment.

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

3. 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** (rare side effect), **feverish** (very common side effect), **short of breath** with a **tight chest or throat** (frequency not known) or have an **itchy rash** (rare side effect). This may be a type of allergic reaction which can be very serious;
- you feel **tired** and **lethargic** (frequency unknown). This may be sign of anemia (a low red blood cell count);
- you have **fever** or other **symptoms of infection** (very common side effect). This may be sign of low white blood cell counts;
- you **bruise** or **bleed** more easily (very common side effect). This may be sign of low platelet count in your blood.

Very common side effects (may affect more than 1 in 10 people)

- feeling sick, being sick, abdominal pain, digestive disorders, diarrhea
- 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 coloration 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 side effects (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 side effects (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 side effects (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 side effects (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 were 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)

Side effects where frequency is not known (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 (chirrhosis)
- transient increase of liver enzymes
- fat, bald or crusty patches of skin (actinin 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 or pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via 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.

4. How to store Doxorubicin a

Keep this medicine out of the sight and reach of children.

Do not use Doxorubicin after the expiry date which is stated on the vial and outer carton after EXP. The expiry date refers to the last day of that month.

Storage conditions

Before opening:

Store in a refrigerator (2-8°C).

After opening:

The product should be used immediately after opening the vial.

After dilution:

Chemical and physical in-use stability after dilution to a concentration of 0.1 mg/ml to 1.0 mg/ml in 9 mg/ml (0.9%) sodium chloride solution for infusion or in 50 mg/ml (5%) glucose solution for infusion has been demonstrated for 24 hours when stored protected from light at 2-8°C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbiological contamination, 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Do not use this medicine if you notice any precipitate in the vials.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

5. Contents of the pack and other information

What Doxorubicin contains

- The active substance is doxorubicin hydrochloride. Each ml of concentrate for solution for infusion contains 2 mg doxorubicin hydrochloride.
 - Each vial with 5 ml contains 10 mg doxorubicin hydrochloride.
 - Each vial with 10 ml contains 20 mg doxorubicin hydrochloride.
 - Each vial with 25 ml contains 50 mg doxorubicin hydrochloride.
 - Each vial with 100 ml contains 200 mg doxorubicin hydrochloride.
- The other ingredients are sodium chloride, hydrochloric acid (E507) and water for injection.

What Doxorubicin looks like and contents of the pack

Doxorubicin is a clear, orange red solution. The solution is supplied in type I glass vials closed with a bromobutyl rubber closure with a flip off aluminium seal. Doxorubicin is available in vials of 5 ml, 10 ml, 30 ml and 100 ml. Each package contains 1 injection bottle.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Agila Specialties UK Limited,
New bridge street House, 30-34 New Bridge Street,
London EC4V 6BJ,
United Kingdom

Manufacturer

Agila Specialties Polska Sp.Z.o.o.
10, Daniszewska Str
03-230 Warsaw
Poland

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The following information is intended for healthcare professionals only:

Doxorubicin 2 mg/ml concentrate for solution for infusion

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 and section 3 of the package leaflet for this medicinal product. The following guidelines should be followed when handling, preparing and disposing of doxorubicin.

For single use only.

Handling

Doxorubicin may NOT be administered by the intramuscular, subcutaneous, oral or intrathecal route.

Further dilution of the appropriate volume of the concentrate with either of 0.9 % sodium chloride solution or 5 % glucose solution is required to a final concentration of between 0.1 mg/ml and 1 mg/ml.

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 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 designate area. Rinse twice with water. Put all cloths into a plastic bag and seal for incineration.

In use stability

Product diluted in 0.9% sodium chloride solution:

The chemical and physical in-use stability after dilution to a concentration of 0.1mg/ml to 1.0mg/ml has been demonstrated for 24 hours when stored protected from light at 2-8°C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbiological contamination, 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 2-8°C, unless reconstitution/dilution has taken place under controlled and validated aseptic conditions.

Product diluted in 5% Glucose solution:

The chemical and physical in-use stability after dilution to a concentration of 0.1mg/ml to 1.0mg/ml has been demonstrated for 24 hours when stored protected from light at 2-8°C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbiological contamination, 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 2-8°C, unless reconstitution/dilution has taken place under controlled and validated aseptic conditions.

Disposal

Single use only. 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 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.