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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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.

What is in this leaflet:

1. What Doxorubicin concentrate for solution for infusion is and what it is used for

The name of your medicine is “Doxorubicin 2 mg/ml Concentrate for Solution for Infusion” but in the rest of the leaflet it will be called ‘Doxorubicin concentrate for solution for infusion’.

Doxorubicin is one of a group of medicines called the anthracyclines. These drugs are also known as cancer drugs, chemotherapy, or "chemo". They are used in the treatment of various cancers to slow or stop the growth of cancer cells. A combination of different types of cancer drugs will often be used to achieve better results and minimize side effects.
Doxorubicin concentrate for solution for infusion is used to treat the following forms of cancer:
- breast cancer
- cancer of the connective tissue, ligaments, bone, muscle (sarcoma)
- cancer develops within the stomach or intestine
- lung cancer
- lymphomas, a cancer affecting the immune system
- leukaemia, a cancer that causes abnormal production of blood cell
- cancer of the thyroid gland
- advance ovarian and endometrial cancer (a cancer of the lining of the uterus or of the uterus)
- bladder cancer
- advance neuroblastoma (a cancer of the nerve cells commonly found in children)
- malignant renal tumour in children (Wilm´s tumour)
- myeloma (cancer of the bone marrow)

2. What you need to know before you use Doxorubicin concentrate for solution for infusion

Do not use Doxorubicin concentrate for solution for infusion
- if you are allergic to Doxorubicin hydrochloride or any of the other ingredients of this medicine (listed in section 6), anthracendiones or to other anthracyclines.

- if you suffer from persistent suppression of the ability of your bone marrow to make blood cells (myelosuppression).
- if you have previously been treated with doxorubicin or similar chemotherapy drugs like, idarubicin, epirubicin or daunorubicin as previous treatment with these similar medicines can increase the risk of side effects with Doxorubicin concentrate for solution for infusion.
- if you suffer from any kind of infection.
- if your liver is not working well.
- if you had a heart attack
- if you have impaired heart function
- if you have serious abnormality of the heart beat (arrhythmia)
- if you are breast-feeding (see also the section "Pregnancy, breast-feeding and fertility").

You should not receive the medicine through a catheter (a thin flexible tube) into your bladder:
- if you are allergic to Doxorubicin hydrochloride or any of the other ingredients of this medicine (listed in section 6), anthracendiones or to other anthracyclines
- if you have a tumour that has grown into the bladder wall
- if you have a urinary tract infection
- if you have bladder inflammation
- if you have blood in your urine (haematuria)
- if you have problems with the insertion of a catheter
- if you are breast-feeding (see also the section "Pregnancy, breast-feeding and fertility").

Warnings and precautions
Talk to your doctor or pharmacist if you have or have had any of the following medical conditions or illnesses:
- poor blood cell production in the bone marrow
- heart problems
- liver disorders
- kidney disorders

You should also tell your doctor:
- if you have ever received doxorubicin or any similar anti-cancer medicine (anthracycline) for the treatment of cancer
- if you have received radiation treatment to the upper body
- if you are currently taking or have recently taken Trastuzumab (a medicine used in the treatment of certain cancers). Trastuzumab can remain in the body for up to 7 months. As trastuzumab may affect the heart, you should not use doxorubicin for up to 7 months after you have stopped taking trastuzumab. If doxorubicin is used before this time, then your heart function should be carefully monitored.

Before starting and during treatment with Doxorubicin concentrate for solution for infusion your doctor will perform the following tests:
- blood counts
- function tests of your heart, liver and kidney

During treatment with Doxorubicin, your bone marrow may no longer be able to make enough blood cells and platelets and your blood count may change; for this reason blood tests must be carried out before and during each treatment. The following symptoms can occur as a result of a shortage of blood cells and/or platelets: fever, infections, blood poisoning, bleeding and tissue damage. The doctor treating you must be contacted immediately in the event of fever.

Skin rash along the vein in which the medicine is administered is not unusual, and can be followed by inflammation of the vein (phlebitis). Hardening or thickening of the vein wall can occur, especially if the

medicine is repeatedly administered in a fine vein. If the medicine should leak from the blood vessel into the surrounding tissue (extravasation), local pain, severe inflammation of the subcutaneous tissue (cellulitis) and tissue damage can occur. Inform a nurse if a burning feeling occurs during the injection: the infusion must be stopped immediately and the needle reintroduced in another vein.
Your doctor will monitor your heart function carefully during the treatment because:

- doxorubicin may damage the heart muscle
- doxorubicin treatment may lead to heart failure after a certain cumulative dose (adding up of single doses)
- the risk for a heart muscle damage is higher if you have previously received medicines that may damage the heart or radiotherapy of the upper body.

This medicinal product is generally not recommended in combination with live, attenuated vaccines. Contact with people recently vaccinated against polio should be avoided.
Inflammation of the mucous membranes (mainly in the mouth, less frequently in the oesophagus) can occur during treatment with doxorubicin. This takes the form of pain or a burning feeling, rash, ulceration of the superficial mucosa (often over the entire side of the tongue or under the tongue), bleeding and infections. Any inflammation in the mouth generally appears soon after administration of the medicine and in severe cases can progress to mucosal ulcers within a few days; in most cases however the patient recovers from this side effect by the 3rd week of treatment.

Nausea, vomiting and occasionally diarrhoea can occur. They can be prevented or relieved by appropriate treatment that your doctor can prescribe.

Reddening of your urine, (which is normal and related to the colour of the medicine). You should inform your doctor if it does not stop in a few days or you think there is blood in your urine. Let your doctor know if you get these symptoms.

Doxorubicin can cause problems with infertility and can damage reproductive cells. Both men and women must use effective contraception during their treatment and for a period after ending treatment with doxorubicin (see the section “Pregnancy, breast-feeding and fertility”). If you wish to become pregnant after treatment with doxorubicin, you must talk to your doctor about genetic counselling and the options to preserve fertility before you start the treatment.

Skin reactions and hypersensitivity reactions:

- Hair loss and interruption of beard growth can occur. This side effect is usually reversible, with complete regrowth of the hair within two to three months after ending the treatment.
- Flushing, discolouration of the skin and nails and hypersensitivity to sunlight can occur.

In rare cases allergic reactions (hypersensitivity) can occur; signs or symptoms of these reactions can range from skin rash and itching (pruritus, urticaria) to fever, chills and anaphylactic shock.

Other medicines and Doxorubicin concentrate for solution for infusion
Tell your doctor if you are taking, have recently taken or might take any other medicines.

The following medications can interact with Doxorubicin concentrate for solution for infusion:

- Other cytostatics (medication against cancer) e.g. trastuzumab, anthracyclines (daunorubicin, epirubicin, idarubicin), cisplatin, cyclophosphamide, ciclosporin, cytarabine, dacarbazine, dactinomycin, fluorouracil, mitomycin C, taxanes (e.g. paclitaxel), mercaptopurine, methotrexate, streptozocin
- Cyclosporine: which can make the effects of doxorubicin stronger and may result in prolonged decrease in bone marrow and blood cells (coma and seizures have also been described with concomitant administration of cyclosporine and doxorubicin)
- Cardioactive drugs (medication to treat heart diseases) e.g. calcium channel blockers, verapamil, and digoxin

- Inhibitors of cytochrome P-450 (drugs that stop the substance cytochrome P-450, which is a important for detoxification of your body, from working: e.g. cimetidine), drugs inducing cytochrome P–450 (e.g. rifampicin, barbiturates including phenobarbital)
- Antiepileptic drugs (e.g. carbamazepine, phenytoin, valproate)
- Antipsychotics: Clozapine (drug used for schizophrenia)
- Warfarin (prevents the clotting of blood)
- Antiretroviral drugs (medication against special forms of viruses).
- Chloramphenicol and sulphonamides (medication against bacteria)
- Amphotericin B (drugs used against fungal diseases)
- Live vaccines (e.g. polio (myelitis), malaria)
- Some medicines effect the concentration and clinical effect of doxorubicin (e.g. St John's Wort)
- Paclitaxel: which can make the effects of doxorubicin stronger

Please note that this can also apply to recently used medicines.

Pregnancy, breast-feeding and fertility

Pregnancy

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 through the placenta and harms the foetus in animal experiments. If you are pregnant, your doctor will give you doxorubicin only if the benefits of the treatment outweigh the potential harm for the unborn child. Tell your doctor immediately if you are pregnant or think you are pregnant.

Women should not get pregnant during treatment with doxorubicin or up to 7 months after treatment. Men should take adequate precautions to ensure that your partner does not become pregnant during your treatment with doxorubicin or up to 4 months after treatment.

Breast-feeding
Do not breast-feed while you are treated with Doxorubicin concentrate for solution for infusion and for at least 14 days after the last dose. The medicine can be passed on to the baby through the breast milk and possibly harm your child.

Fertility
Men should 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.

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

Driving and using machines

Due to the frequent occurrence of nausea and vomiting, driving cars and operation of machinery should be discouraged.

Doxorubicin concentrate for solution for infusion contains Sodium
This medicinal product contains 0.15 mmol (3.5 mg) sodium per ml. To be taken into consideration by patients on a controlled sodium diet. The different pack sizes of this medicinal product contain the following amounts of Sodium:

This medicine contains less than 1 mmol sodium (23 mg) in each 5ml vial, that is to say essentially 'sodium-free'.
This medicine contains 35.42mg sodium (main component of cooking/table salt) in each 10ml vial. This is equivalent to 1.77% of the recommended maximum daily dietary intake of sodium for an adult.
This medicine contains 88.55mg sodium (main component of cooking/table salt) in each 25ml vial. This is equivalent to 4.43% of the recommended maximum daily dietary intake of sodium for an adult.
This medicine contains 177.10mg sodium (main component of cooking/table salt) in each 50ml vial. This is equivalent to 8.85% of the recommended maximum daily dietary intake of sodium for an adult.
This medicine contains 354.20mg sodium (main component of cooking/table salt) in each 100ml vial. This is equivalent to 17.71% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Doxorubicin concentrate for solution for infusion

Method and routes of administrations
Doxorubicin concentrate for solution for infusion can only be given under supervision by a doctor with experience in cancer treatment.

Your doctor will decide about the dose you will receive.
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 3 weeks when used alone. The dosage may need to be reduced to 30-60 mg per square metre of body surface area and the treatment interval prolonged when given in combination with other anti-tumour drugs. Your doctor will advise you of how much you will need. If given weekly the recommended dose is 15 - 20 mg per square metre of body surface area. Your doctor will advise you of how much you will need.

Patients with reduced liver and renal functions
If liver or kidney function is reduced, the dosage should be decreased. Your doctor will advise you of how much you will need.

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

Patient with bone marrow suppression
The dosage may need to be reduced in patient with bone marrow suppression. Your doctor will advise you of how much you need.

Obese patients
The starting dose may be reduced in obese patients or the dose interval may be prolonged. Your doctor will advise you of how much you need and how often.

If you use more Doxorubicin concentrate for solution for infusion than you should
During and after treatment your doctor or nurse will carefully monitor you. The symptoms of an overdose are an extension of doxorubicin's possible side effects. Particularly the blood changes, gastro-intestinal and heart problems. Heart disorders may even occur up to six month after you received the over dose.

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.

If you missed a dose of Doxorubicin concentrate for solution for infusion
Your doctor will decide on the duration of your treatment with Doxorubicin concentrate for solution for infusion. 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 stop using Doxorubicin concentrate for solution for infusion
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.

In certain individuals this medicine can cause a possibly life-threatening severe allergic reaction (anaphylaxis). **Contact a doctor immediately** if you notice the sudden onset of breathing difficulties, swelling of the face and throat and become generally unwell (shock).

Doxorubicin severely reduces the ability of the immune defence system to respond therefore, there is a major risk of infection or infestation that can lead to generalised infection linked with microbes entering the blood (blood poisoning). **Contact a doctor immediately** in the event of high fever because blood poisoning can be fatal.

Other side effects that may occur are as follows:
Very common: may affect more than 1 in 10 people
- Infection
- Loss of appetite (anorexia)
- Inflammation in the mouth (stomatitis)/inflammation of the mucous membranes (mucositis)
- Diarrhoea
- Feeling sick (nausea) or being sick (vomiting)
- Reduction in the number of cells in the blood: red blood cells (anaemia), all or some white blood cells (leukopenia, neutropenia) and platelets (thrombocytopenia)
- Reddening, swelling, numbness, pain and tingling in the palms of the hands and feet (palmoplantar erythrodysesthesia or acral erythema)
- Loss of hair on the head and body (alopecia and interruption of beard growth)
- Fever, feeling weak (asthenia), chills
- Abnormal ECG (this is an electrical trace of your heart)
- Asymptomatic reductions in left ventricular ejection fraction
- Changes in the levels of liver enzymes (transaminases)
- Weight gain in patients with early breast cancer
- Damage to the heart muscle (cardiotoxicity).

Common: may affect up to 1 in 10 people

- Inflammation of the conjunctiva, the membrane that covers the front of the eye and the inside of the eyelids (conjunctivitis)
- Changes in heart function, in particular the heart rhythm (sinus tachycardia), reduction in the amount of blood pumped around the body by the heart (congestive heart failure)
- Inflammation of the oesophagus (oesophagitis)
- Stomach ache

- Itchy rash, rash, discolouration (hyperpigmentation) of the skin and nails
- Blood poisoning
- Redness and swelling may develop at site of injection
- Local side effects when administered into the bladder, such as bladder inflammation (chemical cystitis).

Uncommon: may affect up to 1 in 100 people
- Embolism (blood clot in a blood vessel).

Rare (may affect up to 1 in 1,000 people)
- 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).

Not known: (frequency cannot be estimated from the available data)
- Dehydration
- Increased urea in the blood (hyperuricaemia)
- Blood cancer (acute lymphocytic leukaemia, acute myeloid leukaemia)
- Shock
- Inflammation of the surface of the cornea (keratitis), increased tear production
- Increased heart rate (tachyarrhythmias), loss of nerve impulses from the heart (atrioventricular block and bundle branch block)
- Vein inflammation (phlebitis), total blockage of a vein (thrombophlebitis), flushing, bleeding problems (haemorrhage)
- Irritation or bleeding in the intestines, soreness or ulcers in the mouth, which may not appear until 3-10 days after treatment, discoloration inside the mouth
- Increased sensitivity of the skin to the sunlight
- Inflammation of the large intestine (colitis) and inflammation of the lining of the stomach
- Itchy skin and other skin disorders
- Hypersensitivity of irradiated skin (radiation recall reactions)
- Red coloring of the urine
- Women may also find that their periods stop (amenorrhoea), but their periods should return to normal after medication is stopped. In some cases early menopause can occur.
- In men, doxorubicin may cause an absence or decrease in sperm count (oligospermia, azoospermia), but this may return to normal after medication is stopped.
- Feeling sick or unwell (malaise)
- Liver toxicity
- Temporary increase in liver enzymes
- Condition in which the kidney stops functioning (acute renal failure)

Shortness of breath due to spasm of the muscles of the respiratory tract (bronchospasm).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via

HPRA Pharmacovigilance

Website: www.hpra.ie

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

5. How to store Doxorubicin concentrate for solution for infusion

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 vial or outer carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Keep the vial in the outer carton in order to protect from light.
Do not use this medicine if you notice that the solution is not clear, red and free of particles.

Single use only.

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.

Observe guidelines for handling cytotoxic drugs.

Unopened vials: 18 months

Opened vials: The product should be used immediately after opening the vial.
Chemical and physical in-use stability has been demonstrated in 0.9% sodium chloride injection and 5% dextrose injection for up to 28 days at 2 – 8°C and for up to 7 days at 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.

6. Contents of the pack and other information

What Doxorubicin concentrate for solution for infusion contains:
Doxorubicin concentrate for solution for infusion contains the active ingredient Doxorubicin Hydrochloride.
1 ml contains 2 mg Doxorubicin hydrochloride

Each 5 ml vial contains 10 mg of Doxorubicin hydrochloride.
Each 10 ml vial contains 20 mg of Doxorubicin hydrochloride.
Each 25 ml vial contains 50 mg of Doxorubicin hydrochloride.
Each 50 ml vial contains 100 mg of Doxorubicin hydrochloride.
Each 100 ml vial contains 200 mg of Doxorubicin hydrochloride.

The other ingredients are sodium chloride, hydrochloric acid (for pH adjustment) and water for injections.

What Doxorubicin concentrate for solution for infusion looks like and contents of the pack:

Doxorubicin concentrate for solution for infusion is a clear, red solution, which is practically free from particles.

Pack sizes:
1 × 5 ml vial
1 × 10 ml vial
1 × 25 ml vial
1 × 50 ml vial
1 × 100 ml vial

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Accord Healthcare Ireland Limited
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

Manufacturer

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

Accord Healthcare B.V.,
Winthontlaan 200,
3526 KV Utrecht,
The Netherlands

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Name of the Member State	**Name of the medicine**
United Kingdom (Northern Ireland)	Doxorubicin 2 mg/ml Concentrate for Solution for Infusion
Austria	Doxorubicin Accord 2 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Belgium	Doxorubicin Accord Healthcare 2 mg/ml, solution à diluer pour perfusion/ concentraat voor oplossing voor infusie / Konzentrat zur Herstellung einer Infusionslösung
Bulgaria	Doxorubicin Accord 2 mg/ml Concentrate for Solution for Infusion
Germany	Doxorubicin Accord 2 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Denmark	Doxorubicin Accord
Estonia	Doxorubicin Accord 2 mg/ml
Spain	Doxorubicin Accord 2 mg/ml Concentrado para solución para perfusión
Finland	Doxorubicin Accord 2 mg/ml Infuusiokonsentraatti, liuosta varten/koncentrat till infusionsvätska, lösning
Hungary	Doxorubicin Accord 2 mg/ml koncentrátum oldatos infúzióhoz
Ireland	Doxorubicin 2 mg/ml Concentrate for Solution for Infusion
Italy	Doxorubicina Accord Healthcare Italia 2mg/ml concentrato per soluzione per infusiones
Lithuania	Doxorubicin Accord 2 mg/ml koncentratas infuziniam tirpalui
Latvia	Doxorubicin Accord 2 mg/ml koncentrāts infūziju šķīduma pagatavošanai
The Netherlands	Doxorubicin Accord 2 mg/ml Concentraat voor oplossing voor infusie
Norway	Doxorubicin Accord 2 mg/ml Konsentrat til infusjonsvæke
Poland	Doxorubicinum Accord
Portugal	Doxorrubicina Accord
Romania	Doxorubicinã Accord 2 mg/ml concentrat pentru soluþie perfuzabilã
Sweden	Doxorubicin Accord 2 mg/ml Koncentrat till infusionsvätska, lösning
Slovenia	Doksorubicin Accord 2 mg/ml koncentrat za raztopino za infundiranje

The leaflet was last revised in 12/2023.

The following information is intended for medical or healthcare professionals only

Posology and method of administration
Doxorubicin Injection should be administered only under the supervision of a qualified physician with extensive experience in cytotoxic treatment. Also, patients must be carefully and frequently monitored during the treatment.

Due to the risk of often lethal **cardiomyopathy**, the risks and benefits of the individual patient should be weighted before each application.

Doxorubicin is administered intravenously and intravesically and must not be administered orally, subcutaneously, intramuscularly or intrathecally. Doxorubicin can be administered intravenously as bolus within minutes, as short infusion for up to an hour or as continuous infusion for up to 96 hours.

The solution is given via the tubing of a freely running intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection within 3 to 10 minutes. This technique minimises the risk of thrombophlebitis or perivenous extravasation, which can lead to severe local cellulites, vesication and tissue necrosis. A direct intravenous injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Intravenous administration:
The dosage of doxorubicin depends on dosage regimen, general status and previous treatment of the patient. Dose schedule of doxorubicin hydrochloride administration could vary according to indication (solid tumours or acute leukaemia) and according to its use in the specific treatment regimen (as single agent or in combination with other cytotoxic agents or as a part of multidisciplinary procedures that include combination of chemotherapy, surgical procedure and radiotherapy and hormonal treatment).

Monotherapy
Dosage is usually calculated on the basis of body surface area (mg/m^2). On this basis, a dose of 60 - 75 mg/m^2 body surface area is recommended every three weeks when doxorubicin is used as a single agent.

Combination regimen
When doxorubicin hydrochloride is administered in combination with other antitumour agents with overlapping toxicity, such as high-dose i.v. cyclophosphamide or related anthracycline compounds such as daunorubicin, idarubicin and/or epirubicin, the dosage of doxorubicin should be reduced to 30-60 mg/m^2 every 3 – 4 weeks.

In patients, who cannot receive the full dose (e.g. in case of immunosuppression, old age), an alternative dosage is 15-20 mg/m^2 body surface per week.

Intravesical administration:
Doxorubicin may be used by intravesical instillation for the treatment of superficial bladder carcinoma or in prophylaxis of tumour recurrence after transurethral resection (T.U.R) in patients with high risk of recurrence. The recommended doxorubicin hydrochloride dose for local intravesical treatment of superficial bladder tumours is instillation of 30-50 mg in 25-50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. The optimal concentration is about 1 mg/ml. Generally the solution should be retained intravesically for 1 to 2 hours. During this period the patient should be turned 90° every 15 minutes. The patient should not drink fluids for 12 hours prior to the treatment to avoid undesired dilution with urine (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.

Patients with impaired hepatic function
Since doxorubicin hydrochloride is mainly excreted via liver and bile, the elimination of the medicinal product may be decreased in patients with hepatic function impairment or bile flow obstruction and this could result in severe secondary effects.

General dose adjustment recommendations in patients with hepatic function impairment are based on serum bilirubin concentration:

Serum Bilirubin	Recommended Dose
1.2 – 3.0 mg/100 ml	50%
3.1 – 5.0 mg/100 ml	25%

Doxorubicin is contraindicated in patients with severe liver function disorder.

Patients with impaired renal function
In patients with renal insufficiency (GFR < 10 ml/min), only 75% of the planned dose should be given.

In order to avoid cardiomyopathy, it is recommended that the cumulative total lifetime dose of Doxorubicin (including related drugs such as daunorubicin) should not exceed 450-550mg/m^2 body surface area. If a patient with concomitant heart disease receives mediastinal and/or heart irradiation, prior treatment with alkylating agents, and high-risk patients (with arterial hypertension since > 5 years, with prior coronary, valvular or myocardial heart damage, age over 70 years) a maximum total dose of 400 mg/m^2 body surface area should not be exceeded and the cardiac function of these patients should be monitored.

Dose in children
Dosage in children may need to be reduced, please refer to treatment protocols and the specialist literature.

Obese patients and patients with neoplastic bone marrow infiltration
A reduced starting dose or prolonged dose interval might need to be considered in obese patients and in patients with neoplastic bone marrow infiltration.

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.
Until detailed compatibility information about miscibility is available, Doxorubicin should not be mixed with other medicinal products than 0.9% sodium chloride injection and 5% dextrose injection.

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 28 days at 2 – 8 °C and for up to 7 days at 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.

Disposal

Remnants of the medicinal product as well as all 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Shelf life and storage
Unopened vials: 18 months
Opened vials: The product should be used immediately after opening the vial.
Store in a refrigerator (2°C - 8°C).
Keep the vial in the outer carton in order to protect from light.