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 further questions, please 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 symptoms 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) or to other anthracycline;.
- if you have been told your blood is thin (your bone marrow is not working well).

- if you have previously been treated with doxorubicin or similar chemotherapy drugs like, idarubicin, epirubicin or danuorubicin as previous treatment with these similar medicines can increase the risk of side effects with Doxorubicin concentrate for solution for infusion.
- 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 (in case the medicine is given to you by an administration in to your bladder).
- if there is blood in your urine
- had a heart attack
- impaired heart function
- serious abnormality of the heart beat (arrhythmia)

You should not receive the medicine through a catheter (a thin flexible tube) into your bladder if you have:
- a tumour that has grown into the bladder wall
- an urinary tract infection
- bladder inflammation
- problems with the insertion of a catheter

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

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

Doxorubicin strongly reduces blood cell production in the bone marrow. This may make you more prone to infections or bleeding. It should be made sure that severe infections and/or bleedings can be treated without delay and efficaciously.

Tell your doctor immediately:
- if you feel a stinging or burning pain at the site of injection. Such a pain can occur if the medicine leaks out of the 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.

The levels of uric acid (showing that cancer cells are destroyed) in your blood may be high during treatment. Your doctor will tell you if you need to take any medicine to control this.

- Existing infections should be treated before Doxorubicin concentrate for solution for infusion therapy is started.
- This medicinal product is generally not recommended in combination with live, attenuated vaccines. Contact to persons recently vaccinated against polio should be avoided.
- As Doxorubicin concentrate for solution for infusion is excreted mainly via the liver and in the bile, its excretion can be reduced if liver function is impaired or the bile ducts narrowed, and this can lead to severe secondary side effects.

Doxorubicin concentrate for solution for infusion can turn the urine red. This is not a sign of damage to health.

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 2 mg/ml 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
- Cardioactive drugs (medication to treat heart diseases) e.g. calcium channel blockers, verapamil, and digoxin
- Medicines that lower the uric acid level in your blood
- 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)
- Heparin (prevents the clotting of blood)
- Antiretroviral drugs (medication against special forms of viruses).
- Chloramphenicol and sulphonamides (medication against bacteria)
- Progesterone (e.g. at threatening miscarriage)
- Amphotericin B (drugs used against fungal diseases)
- Live vaccines (e.g. polio (myelitis), malaria)

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

Pregnancy, breast-feeding and fertility

Pregnancy
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.

Breast-feeding
Do not breast-feed while you are treated with Doxorubicin concentrate for solution for infusion. The medicine can be passed on to the baby through the breast milk.
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 and to 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.

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.

Dosage: Your doctor will decide about the dose you will receive.
Do not administer the medicine your self. 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.

Please contact your doctor or nurse immediately if you notice any of the following side effects:

- Feeling dizzy, feverish, short of breath with a tight chest or throat or have an itchy rash. This type of allergic reaction can be very serious.
- Anaemia (a low red blood cell count) that can leave you feeling tired and lethargic.
- White blood cell counts (Which fight infection) can also drop, increasing the chance of infections and raised temperature (fever)
- Platelets (these are cells that help the blood to clot) can be affected which could make you bruise or bleed more easily. It is important to seek medical advice if this happens. Your doctor should test your blood cell count during treatment.
- Doxorubicin may cause decreased activity in your bone marrow. Your doctor should test your blood cell count during treatment.

Frequency:

Common (may affect up to 1 in 10 people)	- cardiomyopathy (heart muscle disease) - ECG (electrocardiogram) changes - bone-marrow suppression(deficiency in blood cells causing infection and bleeding) - changes to the blood count (leukopenia, neutropenia) - nausea (feeling sick) - vomiting (being sick) - mucositis (inflammation of membranes in digestive tract) - stomatitis (inflammation of membranes in the mouth) - anorexia (eating disorder) - diarrhoea – may result in dehydration - chemical cystitis (bladder inflammation) sometimes haemorrhagic (with blood in urine) following administration in to the bladder - alopecia (hair loss) normally reversible - sepsis (bacteria infection) - septicaemia (bacterial infection of blood)
Uncommon (may affect up to 1 in 100 people)	- Ulceration and necrosis (death of cell/tissue) of the colon (intestine) in combination with cytarabine - phlebitis (inflammation of a vein) - gastrointestinal bleeding - abdominal pain

	- local hypersensitivity reaction of the field of radiation - dehydration
Rare (may affect up to 1 in 1,000 people)	- secondary acute myeloid leukaemia (blood cancer developed after treatment for another cancer) when in combination with anti-neoplastic drugs which damage the DNA - tumour lysis syndrome (complications of having chemotherapy) - conjunctivitis (inflammation of the outermost layer of the eye) - urticaria (hives) - exanthema (type of rash) - erythematous reactions (rash-like symptoms) along the vein used for the injection - hyperpigmentation (darkened areas) of the skin and nails - onycholysis (loosening of the nails) - anaphylactic reaction (severe allergic reactions with or without shock including skin rash, pruritis (itching),) - shivering - fever - dizziness
Not known (frequency cannot be estimated from the available data)	- Acute lymphocytic leukaemia (disease in which too many immature white blood cells called lymphoblasts are found in the blood and bone marrow) - acute myelogenous leukaemia (disease in which too many immature blood-forming cells are found in the blood and bone marrow) - Thrombophlebitis (vein inflammation under the skin) - thromoembolism (clot formed in a blood vessel) - decreased amounts of a blood clotting factor (thrombocytes) - shock - chills - Inflammation of food pipe (oesophagitis) - inflammation of the large intestine (colitis) - arrhythmia (irregular heartbeat) - heart failure (loss of cardiac function) - hyperuricaemia (high uric acid level in blood) - bronchospasm (coughing or difficulty in breathing because of narrowing sudden of airways) - pneumonitis (inflammation of lung tissue) - amenorrhoea (absence of menstruation) - oligospermia (low sperm volume) - acute renal (kidney) failure (low urine output/or no urine)keratitis (inflammation of the cornea of the eye) - lacrimation (excessive secretion of tears) - acral erythema (swelling and numbness of the hands and feet) - plantar-palmar dysaesthesia (hand-to-foot syndrome is a distinctive and relatively frequent skin toxic reaction) - excessive pigmentation of oral mucosa - feeling of intense heat (hot flushes) - azoospermia (lack of sperml - Anaemia (reduction of red blood cells) - A stinging or burning sensation at the administration site in relation to extravasation. Extravasation can lead to local death of calls of the tissue which may require surgical measures - liver toxicity - Transient increase of liver enzymes - asthenia (loss or lack of bodily strength; weakness; debility) - Photosensitivity (increased sensitivity of the skin to sun)

Other Side effects: Doxorubicin concentrate for solution for infusion may cause a red colouration of the urine for one or two days after administration. This is normal and nothing to worry about.

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

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 concentrate for solution for infusion

Keep 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.
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 and manufacturer:

Marketing Authorisation Holder
Accord Healthcare Limited
Sage House,
319, Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

Manufacturer
Accord Healthcare Limited
Sage House,
319, Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

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

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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 2 to 15 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 (eg. 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
20-50 micro mole/L	½ normal dose
> 50 micro mol/L	¼ normal dose

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)** with 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
A reduced starting dose or prolonged dose interval might need to be considered in obese patients.

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.