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Package leaflet: Information for the user

Daunorubicin 20 mg Powder for I.V. Injection daunorubicin hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or nurse
- If you get any side effects talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:

1. WHAT DAUNORUBICIN IS AND WHAT IT IS USED FOR

The name of your medicine is Daunorubicin 20 mg Powder for I.V. Injection (called daunorubicin in this leaflet). It belongs to a group of medicines used to treat acute leukaemia.

Daunorubicin works by attacking and destroying the abnormal white blood cells which are present in a person with leukaemia.

Information about Leukaemia

Leukaemia is the name for a number of diseases of the white blood cells, which form part of your blood. These cells are produced in your bone marrow. In leukaemia, the white blood cells multiply in an uncontrolled and abnormal way.

The most common signs of leukaemia are:

- Increased number of white cells in the blood. This causes easy bruising and nose bleeds
- Feeling tired, faint, dizzy, having pale skin. These could be symptoms of anaemia
- Extreme tiredness (exhaustion), and headaches
- Bone and joint pain
- Severe infection and fever

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE DAUNORUBICIN

Before treatment, you should discuss the risks and benefits of this medicine with your doctor.

Do not have daunorubicin if:

- You are sensitive to, or allergic to, daunorubicin or other anthracyclines or any of the other ingredients of this medicine (listed in section 6)

  Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- You have chicken pox or shingles, or you have been in recent contact with anyone who has chicken pox or shingles
- You have an infection, fever or high temperature
- You have any heart problems
- You are pregnant or breastfeeding
- You have a lot of mouth ulcers

Do not have daunorubicin if any of the above applies to you. If you are not sure, talk to your doctor or nurse.

Warnings and precautions

Talk to your doctor or nurse before you are given daunorubicin if:

- You have had radiation treatment to the chest
- You have had any other medicines to treat leukaemia (or cancer)
- You have or have ever had gout
- You have or have ever had kidney stones or any other kidney problems
- You have any liver problems
- You are sexually active, you are advised to use effective birth control to prevent pregnancy during treatment, whether you are male or female.

Before each treatment with daunorubicin, your doctor will do blood tests to check that you have enough white blood cells (which are important for fighting infection) to receive daunorubicin. If you feel you have a fever, please contact your doctor immediately.

Talk to your doctor or nurse during the use of daunorubicin:

- If you notice any pain in your side, blood in your urine or reduced amount of urine. When your disease is very severe, your body may not be able to clear all the waste products from the dying cancer cells. This is called tumour lysis syndrome and can cause kidney failure and heart problems soon after the first dose of daunorubicin. Your doctor will be aware of this and may give you other medicines to help prevent it.
- If you have abdominal pain as a result of inflammation of the bowels (colitis).

A neurological disorder called PRES has been reported when treatment with daunorubicin has been used in combination with other cancer treatments. PRES can cause symptoms such as headache, seizures, lethargy, confusion and disturbed vision. If you experience any of these symptoms you should contact your doctor

If you are not sure if any of the above apply to you, talk to your doctor or nurse before being given daunorubicin.

Other medicines and daunorubicin

Tell your doctor or pharmacist if you are taking, have recently taken or might take any:

- Other medicines that may affect your heart for example, medicines to treat cancer such as 5-fluorouracil, cyclophosphamide, cisplatin, taxanes, calcium channel blockers used to control high blood pressure, chest pain, and irregular heartbeats and if you are receiving chest radiotherapy.
- Other medicines that may affect the bone marrow for example, other cancer treatments, sulphonamide, chloramphenicol (used to treat infection), diphenylhydantoin (used to treat epilepsy), amidopyrine-derivative (used to relieve pain), antiretroviral agents (used to treat HIV infection) may alter the formation of blood cells
- Other medicines that may affect your liver e.g barbiturates (drugs used in epilepsy or sleep disorders) and rifampicin (a drug used to treat TB - Tuberculosis)
- Live attenuated vaccines

Pregnancy, breast-feeding and fertility

Do not have daunorubicin if you are pregnant, might become pregnant or think you might be pregnant as daunorubicin can be very damaging to your unborn baby (embryo). If pregnancy occurs during treatment this should be discussed with your doctor.

Both female and male patients must take **special precautions** in their sexual activity if there is any possibility for pregnancy to occur:

- **For a girl or woman of childbearing age:**

You must have a negative pregnancy test before treatment and each month during treatment. This should be discussed with your doctor.

- **For men:**

Do not have sex with a pregnant woman unless you **use a condom.** This will lessen the possibility for daunorubicin to be left in the woman's body.

You and your female partner must each use an effective contraceptive during the time you are taking daunorubicin and for 6 months after stopping treatment. This should be discussed with your doctor.

Men who wish to father children in the future should seek advice about freezing sperm before treatment with daunorubicin is started.

If you are a woman who is **breast-feeding,** you must not take daunorubicin. Discontinue breast-feeding before starting to take daunorubicin.

Driving and using machines

You may feel and/or be sick after being given this medicine, therefore special care should be taken when driving or using machines.

There is no information available about how daunorubicin might affect your ability to drive or use machines.

3. HOW YOU WILL BE GIVEN DAUNORUBICIN

How daunorubicin is given

- Daunorubicin is a medicine used in hospitals
- It will be given to you by a doctor or nurse as an injection into one of your veins
- It will be given over about 20 minutes (this is called an intravenous infusion)

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Daunorubicin 20 mg Powder for I.V. Injection daunorubicin hydrochloride

For the Medical and Pharmaceutical Professions only

STORE BELOW 25ºC PROTECT FROM LIGHT.
Solutions of Daunorubicin should be freshly prepared, store at 2-8ºC in the dark and use within 24 hours.

PRESENTATION

Daunorubicin is a microcrystalline orange-red hygroscopic sterile powder supplied in vials containing the equivalent of 20 mg daunorubicin (as hydrochloride) and mannitol as a stabilising agent.

INDICATIONS

Daunorubicin is an anthracycline glycoside antibiotic and a potent antileukaemic agent. It also has immuno suppressant effects. The exact mechanism of antineoplastic action of daunorubicin is uncertain but may involve binding to DNA by intercalation between base pairs and inhibition of DNA and RNA synthesis by template disordering and steric obstruction. Daunorubicin is most active in the S-phase of cell division but is not cycle phase-specific. Tumour cell cross resistance has been observed between daunorubicin and doxorubicin.

No controlled paediatric studies have been conducted. The literature mentions the use of daunorubicin in treatment regimens for ALL and AML, including paediatric age groups. However, due to the ongoing search for a balance in gain or maintenance of efficacy and a decrease in toxicity, the use of daunorubicin in the treatment of paediatric ALL and AML is fluctuating in clinical practice, mainly depending on risk stratification and specific subgroups. Published studies suggest no differences in safety profile between paediatric patients and adults.

PHARMACOKINETICS

Daunorubicin is rapidly taken up by the tissues, especially by the kidneys, spleen, liver and heart. It does not cross the blood-brain barrier, subsequent release of drug and its metabolites from the tissue is slow (t1/2 = 55 hours). Daunorubicin is rapidly metabolised in the liver. The major metabolite daunorubicinol is also active. Daunorubucin is excreted slowly in the urine, mainly as metabolites with 25% excreted in the first 5 days. Biliary excretion also makes a significant (40%) contribution to elimination.

DOSAGE AND ADMINISTRATION

Daunorubicin is extremely irritating to tissues and may only be administered intravenously.

Do not administer by the intramuscular or subcutaneous route.

The contents of a vial should be reconstituted with 4ml water for injections giving a concentration of 5mg per ml. The calculated dose of Daunorubicin should be further diluted with normal saline to give a final concentration of 1mg per ml. This solution should be injected over a 20 minute period into the tubing, or side-arm, of a well placed, rapidly flowing i.v. infusion of normal saline (to minimise extravasation and possible tissue necrosis). Alternatively, the Daunorubicin may be added to a minibag of sodium chloride injection 0.9%w/v and this solution infused into the side-arm of a rapidly flowing infusion of normal saline.

Adults: 40-60mg/m^2 on alternate days for a course of up to three injections for the induction of remissions.
Acute myelogenous leukaemia:
The recommended dose is 45mg/m^2.
Acute lymphocytic leukaemia:
The recommended dose is 45mg/m^2

Paediatric patients:

Daunorubicin dosage for children (over 2 years) is usually calculated based on the body surface area and adjusted to meet the individual requirements of each patient, on the basis of clinical response and the patients' haematological status. Courses may be repeated after 3 to 6 weeks.

Current specialised protocols and guidelines should be consulted for appropriate treatment regimen.

For children over 2 years the maximal cumulative dose is 300 mg/m^2.

For children under 2 years of age (or below 0.5m^2 body surface area), the maximum cumulative dose is 10mg/kg.

Elderly:

Daunorubicin should be used with care in patients with inadequate bone marrow reserves due to old age. A reduction of up to 50% in dosage is recommended.

The number of injections required varies widely from patient to patient and must be determined in each case according to response and tolerance.

Daunorubicin should be administered through a large vein and the infusion should be kept free flowing. When second or subsequent injections are given, the doses and the time intervals depend on the effect of the previous doses and must be the subject of careful deliberation, examination of the peripheral blood and, under some circumstances, of the bone marrow.

The effect of Daunorubicin on the disease process and on the normal blood precursors cannot be exactly predicted for any particular case. The difference between incomplete treatment, a satisfactory remission, and overdosage with possible irreversible aplasia of the bone marrow depends on the correct choice of dosage, time intervals and total number of doses. The dosage should be reduced in patients with impaired hepatic or renal function. A 25% reduction is recommended in patients with serum bilirubin concentrations of 20-50 µmol/l or creatinine or above 105-265 µmol/l. A 50% reduction is recommended in cases with serum bilirubin concentrations of above 50 µmol/l or creatinine or above 265 µmol/l.

CONTRA-INDICATIONS

Do not use in patients recently exposed to, or with existing chicken pox or herpes zoster.

PRECAUTIONS AND WARNINGS

Daunorubicin should be used under direction of a clinician conversant with the management of acute leukaemia and cytotoxic chemotherapy. The haematological status of patients should be monitored regularly.

Daunorubicin which might depress the bone marrow to the point where anti-infective agents would no longer be effective. If during Daunorubicin treatment, the patient becomes febrile treatment with broad spectrum antibiotics should be initiated. If facilities are available, patients should be treated in a germ-free environment or, where this is not

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possible, reverse barrier nursing and aseptic precautions should be employed.

Anti-infective therapy should be employed in the presence of suspected or confirmed infection and during a phase of aplasia. It should be continued for some time after the marrow has regenerated. Care should also be used in patients at risk of infection.

Rapid destruction of a large number of leukaemia cells may cause a rise in the blood uric acid or urea (tumour lysis syndrome) and so it is a wise precaution to check these concentrations three or four times a week during the first week of treatment. Fluids should be administered and allopurinol used in severe cases to prevent the development of hyperuricaemia.

Patients with heart disease should not be treated with this potentially cardiotoxic drug. Cardiotoxicity, if it occurs, is likely to be heralded by either a persistent tachycardia, shortness of breath and swelling of feet and lower limbs, or by minor changes in the electrocardiogram and for this reason an electrocardiographic examination should be made at regular intervals during treatment. Cardiotoxicity usually appears within 1 to 6 months after initiation of therapy. It may develop suddenly and not be detected by routine ECG. It may be irreversible and fatal but responds to treatment if detected early.

The risk of congestive heart failure increases significantly when the total cumulative dosage exceeds 600mg/m^2 in adults, 300mg/m^2 in children over 2 years or 10mg/kg in children under 2 years. Cardiotoxicity may be more frequent in children and the elderly. The dosage should be modified if previous or concomitant cardiotoxic drug therapy is used. Daunorubicin should be used with care in patients at risk of hyperuricaemia (e.g. in the presence of gout, urate and renal calculi), tumour cell infiltration of the bone marrow and in patients with inadequate bone marrow reserves due to previous cytotoxic drug or radiation therapy. The cumulative dose of Daunorubucin should be limited to 400mg/m^2 when radiation therapy to the mediastinum has been previously administered. The dose of Daunorubicin should not be repeated in the presence of bone marrow depression or buccal ulceration.

Care should be taken to avoid extravasation during intravenous administration. All steps should be taken to avoid tissuing and bandages should not be used. Facial flushing or erythematous streaking along the vein indicates too rapid injection. If tissue necrosis is suspected, the infusion should be stopped immediately and resumed in another vein. Where extravasation has occurred, an attempt should be made to aspirate the fluid back through the needle. The effected area may be injected with hydrocortisone. Sodium bicarbonate (5ml of 8.4% w.v solution) may also be injected in the hope that through pH changes the drug will hydrolyse. The opinion of a plastic surgeon should be sought as skin grafting may be required.

Application of ice packs may help to decrease local discomfort and also prevent extension. Liberal application of corticosteroid cream and dressing the area with sterile gauze should then be carried out.

USE IN PREGNANCY

Daunorubicin crosses the placenta and experiments in animals have shown it to be mutagenic, carcinogenic and teratogenic.

There is also the possibility that treatment during pregnancy may produce delayed effects in the offspring.

If appropriate, the mother should be offered the opportunity of a therapeutic abortion.

Owing to potential toxic risks to infants, breastfeeding should be discontinued during treatment.

ADVERSE REACTIONS

Bone marrow depression: in every patient bone marrow function will be depressed by treatment with Daunorubicin and in a variable proportion of cases, severe aplasia will develop. The consequence may include severe infection and opportunistic infection. Leucopenia is usually more significant than thrombocytopenia. The nadir for leucopenia usually occurs between 10-14 days and recovery occurs gradually over the next 1-2 weeks. Bone marrow depression must be anticipated in every case by eliminating infection before the treatment, by isolating the patient from infection during the treatment and by means of supportive therapy. This includes the continuous administration of anti-infective agents, the administration of platelet-rich plasma or fresh whole blood transfusion and, under some circumstances, the transfusion of white cell concentrates.

Cases of colitis, enterocolitis and neutropenic enterocolitis (typhlitis) have been observed in patients treated with daunorubicin. Treatment discontinuation and prompt appropriate medical treatment are recommended.

Other less serious adverse reactions that have been reported (in order of reducing frequency) are: stomatitis, alopecia, phlebitis, fever, anaemia, nausea, vomiting, mucositis, diarrhoea and rash. The urine may be temporarily coloured red after treatment.

OVERDOSE

Although no cases have been reported to our knowledge, overdosage may result in drastic myelosuppression and severe cardiotoxicity with or without transient reversible ECG changes leading to congestive heart failure.

Treatment should be supportive and symptomatic.

PHARMACEUTICAL PRECAUTIONS

Vials containing Daunorubicin should be stored below 25ºC and protected from light. Solutions of Daunorubicin should be used immediately after preparation or stored at 2-8ºC and used within 24 hours. The solutions should be protected from light. The reconstituted solution does not contain an antimicrobial preservative. Daunorubicin solutions are unstable above pH8, decomposition being indicated by a change from red to blue-purple colour.

Daunorubicin injection is compatible with sodium chloride injection 0.9%. However a precipitate may form immediately if the solution is mixed with heparin sodium injection or dexamethasone sodium phosphate injection.

LEGAL CATEGORY: POM and PACKAGE QUANTITIES:

Box of 1 x 20 mg and 10 x 20 mg vials.

FURTHER INFORMATION

Spill or Leak Procedures: Daunorubicin injection may be neutralised with sodium hypochlorite prior to disposal of unused drug or if a vial is accidentally broken.

The neutralised drug can be disposed of in the sink.

SPECIAL PROTECTION INFORMATION

Daunorubicin should only be handled by staff experienced with cytotoxic drugs. Further information on handling is available from the Marketing Authorisation holder.

- It should never be given as a single injection under the skin or into a muscle
- The site of injection should not be covered or bandaged

Tell your doctor or nurse straight away if:

- You have any pain, swelling or warmth around the vein where daunorubicin is being injected
- You notice that your face is red while the injection is being given to you. This may be a sign that the injection is being given too quickly

How much daunorubicin will be given

- The exact dose will be determined by your doctor. It will depend on your age, height, weight and your general medical condition. The usual dose for a person weighing 70kg (11 stone) would be about 80mg
- Your course of treatment may be altered, depending on how your body reacts to the medicine
- Daunorubicin may be given alone or in combination with other medicines to treat or prevent side effects

Tests while having daunorubicin

Your condition will be closely monitored during treatment. This may involve blood, urine tests or heart monitoring (called ECG).

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody who is given this medicine will be affected in the same way. If you are worried about side effects you should discuss them with your doctor, who will explain the risks and benefits of your treatment.

Some of the side effects can be lessened or treated by other medicines or therapy.

Tell your doctor or nurse straight away if:

- You have pain, swelling or warmth in or around the vein where daunorubicin is being injected
- You have a red face while daunorubicin is being injected. This may be a sign that the injection is being given too quickly
- You get fevers, chills or other signs of infection, which sometimes can be fatal
- You have any severe infections, such as those of the blood (sepsis), which may also cause low blood pressure (septic shock, a life-threatening form of sepsis) or inflammation of the lungs (pneumonia)
- You have difficulty in breathing
- You have swelling of the feet or legs
- You have an uneven or fast heart beat
- You have black or tarry bowel motions
- You are being sick (vomiting) and bring up blood or dark brown coffee-coloured granules
- You notice any unusual bleeding or bruising
- You develop a neurological disorder called Posterior Reversible Encephalopathy Syndrome (PRES, also known as Reversible Posterior Leukoencephalopathy Syndrome, RPLS) Symptoms include a severe or persistent headache, abnormal vision (such as blurred vision or vision loss), seizures (fits), confusion or memory loss or abnormal behaviour.

Tell your doctor or nurse if you notice any of the following side effects:

- You feel sick (nausea) or are sick (vomit)
- You have diarrhoea
- You have inflammation of the bowel
- You have a skin rash
- You have sores in the mouth or on the lips

Other side effects include:

- Decreased numbers of different types of blood cells (granulocytopenia, leukopenia and neutropenia, anaemia) which may cause tiredness, fever or increased risk of bleeding
- Leukaemia (a type of blood cancer) and other cancers may occur in patients who are treated with daunorubicin together with certain other anticancer treatments
- Reduced number of white blood cells (which are important for fighting infection) associated with fever, including fatal cases
- Changes in metabolism caused by dying cancer cells releasing their contents into the bloodstream (tumour lysis syndrome)
- Feeling very dry and thirsty (dehydration)
- Inflammation of mucous membranes (mucositis), of the mouth with areas of painful erosions, ulceration and bleeding (stomatitis) and of the oesophagus (oesophagitis)
- Loss of appetite
- Increased pigmentation (hyperpigmentation) of skin and nails
- Daunorubicin can make your urine turn red for a couple of days after each dose
- Medicines like daunorubicin often cause temporary loss of hair. After your treatment finishes your hair should grow back
- Disease of the bone marrow
- Infections, which sometimes can be fatal

There have been reports of secondary tumours (secondary leukaemia) following use of daunorubicin in combination with other anti-cancer drugs.

After stopping treatment

After you have finished your course of treatment, you may still get side effects. Tell your doctor or nurse straightaway if:

- You have difficulty in breathing
- You have swelling of the feet or legs
- You get an uneven or fast heart beat

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search from MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE DAUNORUBICIN

- Keep this medicine out of the sight and reach of children.
- Daunorubicin should not be used after the expiry date which is stated on the carton. The expiry date refers to the last day of the month.
- The vials of powder should be kept at room temperature and protected from light.
- The daunorubicin solutions made up from the powder should be stored at between 2 - 8°C, protected from light and used within 24 hours.
- Following the injection, daunorubicin will be disposed of carefully by the doctor or nurse.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Daunorubicin 20 mg Powder for I.V. Injection contains:

The active ingredient is daunorubicin hydrochloride. Each vial contains 20 mg of daunorubicin. Each vial also contains mannitol.

What Daunorubicin 20 mg Powder for I.V. Injection looks like and contents of the pack:

Daunorubicin 20 mg Powder for I.V. Injection comes as a vial containing a red powder. The solution prepared with this powder is also red.

The vials are available in packs of 1 and 10 vials.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder

Zentiva Pharma UK Limited,
12 New Fetter Lane,
London EC4A 1JP,
United Kingdom

Manufacturer

Cenexi - Laboratoires Thissen S.A.
Braine-l'Alleude,
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