CERUBIDIN® 20mg

Powder for Concentrate for Solution for Infusion

daunorubicin

Is this leaflet hard to see or read?
Phone 01 403 5600 for help.

Patient Information Leaflet

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or nurse
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If any of the side effects gets serious, or if you notice any side effects not listed in them leaflet, please tell your doctor or pharmacist

In this leaflet:

1. WHAT CERUBIDIN IS AND WHAT IT IS USED FOR

The name of your medicine is Cerubidin 20mg Powder for Concentrate for Solution for Infusion (called Cerubidin in this leaflet).
It belongs to a group of medicines used to treat acute leukaemia.
Cerubidin is an immunosuppressant drug that works by attacking and destroying the abnormal white blood cells which are present in a person with leukaemia. Sometimes immunosuppressant drugs can make you susceptible to serious infections.
Daunorubicin in combination with other medicinal products can be used in children with acute lymphocytic blood cancer (acute lymphocytic leukemia) and acute myeloid blood cancer (acute myeloid leukemia).

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 ARE GIVEN CERUBIDIN

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

Do not have Cerubidin if:

- You are sensitive to or allergic to Cerubidin or any of the other ingredients of Cerubidin (listed in Section 6 below)
  Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- You have an infection, fever or high temperature. Your doctor will examine you to make sure you do not have any infection before you start treatment with Cerubidin.
- You have chicken pox or shingles, or you have been in recent contact with anyone who has chicken pox or shingles
- You are pregnant or breast-feeding
- You have a lot of mouth ulcers

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

Warnings and Precautions

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

- You have had radiation treatment to the chest
- You have any heart problems
- 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

Hyperuricaemia (high uric acid levels) can occur with Cerubidin treatment. This can occur as a result of a metabolic disorder (Tumor lysis syndrome), symptoms of which can also include fever, chills and feeling extremely tired.
There have also been reports of gastrointestinal disorders such as colitis (inflammation of the colon) and enterocolitis (inflammation of the digestive tract). Treatment should be stopped should these symptoms occur.
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.
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. In case you experience fever, please contact your doctor immediately.
If you are not sure if any of the above apply to you, talk to your doctor, nurse or pharmacist before being given Cerubidin.

Pregnancy and breast-feeding

Do not have Cerubidin if:

- You are pregnant, might become pregnant or think you might be pregnant
- You are breast-feeding or planning to breast-feed

Cerubidin is teratogenic which means it may cause birth defects if used during pregnancy and/or breast-feeding. Ask your doctor, nurse or pharmacist for advice before taking any medicine, if you are pregnant or breast-feeding.

Driving and using machines

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

3. HOW YOU WILL BE GIVEN CERUBIDIN

How Cerubidin is given

- Cerubidin is a medicine used in hospitals
- It will be given to you by a doctor or nurse as an infusion into one of your veins
- It will be given over about 20 minutes (this is called an intravenous infusion)
- It should never be given as a single infusion under the skin or into a muscle
- The site of infusion 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 Cerubidin is being infused
- You notice that your face is red while the Infusion is being given to you. This may be a sign that the infusion is being given too quickly

How much Cerubidin will be given

Cerubidin 20mg Powder for Concentrate for Solution for Infusion

Daunorubicin Hydrochloride

For the Medical and Pharmaceutical Professions only Please refer to full Summary of Product Characteristics before prescribing

Do not store above 25°C. Store in the original container. If prepared aseptically, the reconstituted solution should be stored at 2 - 8°C protected from light and used within 24 hours. Cerubidin diluted in infusion medium, should be used immediately.

Presentation

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

Dosages and administration

Cerubidin 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 Cerubidin should be further diluted with normal saline to give a final concentration of 1mg per ml.
This solution should be infused over a 20 minute period into the tubing, or a side-arm of a well placed, rapidly flowing i.v. infusion of normal saline (to minimise extravasation and possible tissue necrosis). Alternatively, the Cerubidin 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.
The solution is given via the tubing of a freely-running intravenous infusion, taking 20 minutes over the infusion. This technique minimises the risk of thrombosis or perivenous extravasation, which can lead to severe cellulitis and vesication.
Adults: 40 - 60mg/m2 on alternate days for a course of up to three infusions.
Acute Myelogenous Leukaemia and Acute Lymphocytic Leukaemia: 45mg/m2/day is the recommended dose.
Children: Cerubidin dosage for children (over 2 years) is usually calculated based on the body surface area and adjusted to meet individual requirements of each patient, on the basis of clinical response and the patient's haematological status. Courses may be repeated after 3 to 6 weeks.
Current specialized protocols and guidelines should be consulted for appropriate treatment regimen.
• Children over 2 years: The recommended dose is 30 to 60 mg/m2 daily for 3 to 5 days. Maximum cumulative dose is 300 mg/m2
• Children under 2 years of age (or below 0.5 m2) body surface area), the recommended dose is 1 mg/kg/day. Maximum cumulative dose is 10 mg/kg
Elderly: Use with care in patients with inadequate bone marrow reserves. A dosage reduction of up to 50% is recommended.
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 1.2-3mg/100ml and a 50% reduction in cases with serum bilirubin or creatinine concentrations above 3 mg/100ml.

The number of infusions required varies widely from patient response and tolerance.
Daunorubicin should be administered with caution when the neutrophil count is <1,500/mm3. Daunorubicin dose reduction should be considered in case of severe neutropenia.
Cerubidin/Daunorubicin is extremely irritating to tissues and may only be administered intravenously after dilution.
Cerubidin/Daunorubicin should be administrated through a large vein and the infusion should be kept free flowing.
When second or subsequent infusions are given, the doses must be the subject of careful deliberation, examination of the peripheral blood and, under some circumstances, of the bone marrow.
The effect of Cerubidin/Daunorubicin on the disease process and on normal blood precursors cannot be exactly predicted for any particular case. The difference between the 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.

Contra-indications

Do not
• Use in the management of non-malignant disease
• Use in the presence of acute infections
• Use in patients with marked marrow depression unless considered essential by the physician/oncologist
• Use in patients in the presence of oropharyngeal ulceration
• Use in patients recently exposed to, or with existing chicken pox or herpes zoster

Precautions and warnings

• Daunorubicin should only be administered under the direction of a specialist having the facilities for regular monitoring of clinical, biochemical and haematological effects during and after administration.
• Daunorubicin has been shown to be carcinogenic in animals. The possibility of a similar effect should be borne in mind when designing the long-term management of the patient.
• Rapid destruction of a large number of leukaemia cells may cause a risk in the blood uric acid or urea and so it is 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.
Daunorubicin treatment may lead to hyperuricaemia as a consequence of tumour lysis syndrome.
Infections should be treated before the start of daunorubicin therapy. If during daunorubicin treatment a patient becomes febrile (regardless of the neutrophil count), treatment with broad spectrum antibiotics should be initiated.
Daunorubicin produces bone marrow depression. Daunorubicin should be administered with caution when the neutrophil count is < 1,500/mm3. Febrile neutropenia has been reported when daunorubicin is given in combination with other antineoplastic treatments.
Monitoring of blood counts prior to and during daunorubicin treatment is recommended, and hematological abnormalities should be treated promptly.
Cases of colitis, entercolitis and neutropenic entercolitis (typhlitis) have been reported in patients treatment with daunorubicin. Treatment discontinuation and prompt appropriate medical management are recommended.
Posterior reversible encephalopathy syndrome (PRES):
Cases of PRES have been reported with daunorubicin used in combination chemotherapy. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. In patients with PRES, the discontinuation of daunorubicin treatment should be considered.

5926300-M

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Information

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Secondary malignancies have been reported when daunorubicin was given in combination with other antineoplastic treatments known to be associated with secondary malignancies. Secondary malignancies (including leukemia) may occur during daunorubicin-containing therapy, or several months or years after the end of therapy. Patients should be monitored for secondary malignancies .
• Extreme caution should be exercised when using the product in patients with cardiac disorders or in the elderly. Cardiotoxicity if it occurs is likely to be heralded by either a persistent tachycardia, shortness of breath, 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 the treatment. Cardiotoxicity usually appears within 1 to 6 months after initiation of the 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 600 mg/m2 body surface area in adults, 300 mg/m2 in children over 2 years or 10 mg/kg body-weight 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 daunorubicin should be limited to 400 mg/m2 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 to rapid infusion. 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 affected area may be injected with hydrocortisone. Sodium bicarbonate (5 mls of 8.4%) 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 decrease local discomfort and also prevent extension. Liberal application of corticosteroid cream and dressing the area with sterile gauze should then be carried out. Each patient should be given a clinical and bacteriological examination to determine whether infection is present; any infection should be adequately eliminated before treatment with Daunorubicin which might depress the bone marrow to the point where anti-infective agents would no longer be effective. If facilities are available, patients should be treated in a germ-free environment or, where it is not 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.
• Personnel handling this product should wear protective clothing and be trained in good technique for handling.

Use in pregnancy
Daunorubicin has been shown to be teratogenic. The product should not be used in pregnancy unless considered absolutely essential by the physician. Daunorubicin should not be administered to mothers who are breast-feeding infants.

Overdosage
Treatment is supportive and symptomatic.

Pharmaceutical Precautions
Do not store above 25°C. Store in the original container. If prepared aseptically, the reconstituted solution should be stored at 2-8°C protected from light and used within 24 hours. The shelf expiry date for this product shall not exceed 36 months from the date of first opening. Cerubidin solution diluted in infusion medium should be used immediately.
The reconstituted product is incompatible with heparin sodium injection and dexamethasone sodium phosphate injection.

Instructions for Use/Handling
The contents of the vial should be reconstituted with water for injections Ph.Eur. 4ml to give a solution of concentration 5 mg per ml. The calculated dose of Cerubidin should be further diluted with normal saline to give a final concentration of 1mg per ml. Once diluted, use immediately. The solution should be infused over a 20 minute period into the tubing, or side, of a well placed, rapidly flowing i.v. infusion of normal saline (to minimise extravasation and possible tissue necrosis). Alternatively, the Cerubidin 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.

Special Protection Information.
'Cerubidin' should only by handled by staff experienced with cytotoxic drugs. Reconstitution should be carried out in a designated area. Protective clothing (including gloves and eye protection) should be worn. Double gloving is recommend for dealing with major spillage's. Waste should be disposed of carefully in suitable separate containers, clearly labelled as to their contents (it should be noted that the patients body fluids and excreta will contain appreciable amounts of antineoplastic agents and they should be treated a hazardous waste). All staff exposed to Cerubidin should be recorded and monitored.
Pregnant staff should not handle 'Cerubidin'. Spill or Leak Procedures: Daunorubicin infusion 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.

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

Product Authorisation Number:
PA 540/96/1

sanofi-aventis Ireland Ltd., T/A SANOFI
Citywest Business Campus,
Dublin 24,
Republic of Ireland.

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• 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 (12 stone) would be about 80mg
• Your course of treatment may be altered, depending on how your body reacts to the medicine
• Cerubidin may be given alone or in combination with other medicines to treat or prevent side effects

Tests while having Cerubidin
Your condition will be closely monitored during treatment. This may involve regular blood, urine tests or heart monitoring (called ECG).
If you have any questions about your course of treatment ask your doctor, pharmacist or nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cerubidin 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, nurse or pharmacist straight away if:
• You have pain, swelling or warmth in or around the vein where Cerubidin is being infused
• You have a red face while Cerubidin is being infused. This may be a sign that the infusion is being given too quickly
• You get fevers, chills or other signs of infection
• 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

Tell your doctor, nurse or pharmacist if you notice any of the following side effects:
• You feel sick (nausea) or are sick (vomit)
• You have diarrhoea
• You have a skin rash
• You have sores in the mouth or on the lips

Other side effects include:
• Inflammatory disease of the (large) bowel
• Serious infections (sepsis, septic shock and pneumonia) , which sometimes can be fatal
• Secondary leukaemia - when used in combination with other antineoplastics
• Tumor lysis syndrome, a metabolic disorder
• Colitis, inflammation of the colon
• Enterocolitis, inflammation of the digestive tract
• Disease of the bone marrow
• Cerubidin can make your urine turn red for a couple of days after each dose
• Medicines like Cerubidin often cause temporary loss of hair. After your treatment finishes your hair should grow back
• People who have previously had radiation therapy may suffer from 'radiation recall' which occurs during or shortly after certain anti-cancer drugs are given. Symptoms of this include redness of the skin and possible blistering, over the area that received the radiation treatment. This reaction may last for a few hours or even days.
• Cerubidin can cause weakness of the muscles of the heart (cardiotoxicity). This can happen between 1 and 6 months from starting treatment and may be irreversible and fatal, but responds to treatment if detected early. Your condition will be closely monitored during your treatment to help prevent this complication from occurring.

Frequency not known:
• A neurologic disorder called Posterior Reversible Encephalopathy Syndrome (PRES, also known as Reversible Posterior Leukoencephalopathy Syndrome, RPLS) with symptoms such as abnormal behaviour, headache, abnormal vision, seizures (fits), or confusion, including fatal cases.
• 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.

Tell your doctor, nurse or pharmacist if any of the side effects gets serious, lasts longer than a few days, or if you notice any side effects not listed in the leaflet.

After stopping treatment
After you have finished your course of treatment, you may still get side effects. Tell your doctor, nurse or pharmacist 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, 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

5. HOW TO STORE CERUBIDIN

Keep this medicine in a safe place out of the reach and sight of children.
Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.
The vials should not be stored above 25°C. Store in the original container. Reconstituted solutions of Cerubidin should be stored for up to 24 hours at 2-8°C and protected from light. Cerubidin solution diluted in infusion medium, should be used immediately.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Cerubidin contains
The active substance is daunorubicin hydrochloride. Each vial contains 20mg of daunorubicin as daunorubicin hydrochloride. The other ingredient is mannitol.

What Cerubidin looks like and contents of the pack
Cerubidin 20mg Powder for Concentrate for Solution for Infusion 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.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
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Information
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