

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cerubidin 20 mg Powder for Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Daunorubicin Hydrochloride equivalent to Daunorubicin 20 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Concentrate for Solution for Infusion.

A microcrystalline, orange-red, sterile powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an antimitotic and cytotoxic for the induction of remissions in acute lymphocytic and myelogenous leukaemias.

Daunorubicin, as part of combination regimen, is indicated for the treatment of acute lymphocytic leukemia and acute myeloid leukemia in children.

4.2 Posology and method of administration

For intravenous administration only.

The solution is given *via* the tubing of a freely running intravenous infusion, over a 20 minute period. 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:

45mg/m²/day is the recommended dose.

Acute Lymphocytic Leukaemia:

45mg/m²/day is the recommended dose.

Pediatric patients:

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.

For children over 2 years the maximum cumulative dose is 300 mg/m².

For children under 2 years of age (or below 0.5 m² body surface area), the 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.

Daunorubicin should be administered with caution when the neutrophil count is $<1,500/\text{mm}^3$.

Daunorubicin dose reduction should be considered in case of severe neutropenia.

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

Cerubidin/Daunorubicin is extremely irritating to tissues and may only be administered intravenously after dilution.

Cerubidin/Daunorubicin should be administered through a large vein and the infusion should be kept free flowing. When second or subsequent infusions are given, the doses and time intervals on the effect on 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 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.

4.3 Contraindications

1. Use in the management of non-malignant disease.
2. Use in the presence of acute infections.
3. Use in patients with marked marrow depression unless considered essential by the physician/oncologist.
4. Use in patients in the presence of oropharyngeal ulceration.
5. Use in patients recently exposed to, or with existing chicken pox or herpes zoster.
6. Use via intramuscular or subcutaneous routes.

4.4 Special warnings and precautions for use

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.

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 $600 \text{ mg}/\text{m}^2$ body surface area in adults, $300 \text{ mg}/\text{m}^2$ in children over 2 years or $10 \text{ mg}/\text{kg}$ bodyweight 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), tumor 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 $400 \text{ mg}/\text{m}^2$ 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.

Rapid destruction of a large number of leukaemia cells may cause a rise in the blood uric acid or urea 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.

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 $< 1,500/\text{mm}^3$. 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 (see sections 4.2 and 4.8).

Cases of colitis, enterocolitis and neutropenic enterocolitis (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.

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 (see section 4.8).

Care should be taken to avoid extravasation during intravenous administration. All steps should be taking to avoid tissue and bandages should not be used. Facial flushing or erythematous streaking along the vein indicates too 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 ml 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 handling techniques.

4.5 Interaction with other medicinal products and other forms of interactions

None known.

4.6 Fertility, pregnancy and lactation

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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, confusion, seizures and visual disturbances have been observed in patients treated with daunorubicin combination therapy (see section 4.4). Therefore, patients should be warned of the possible impact of the side effects on their ability to drive or use machines, and be advised not to drive or use machines if they experience these side effects during treatment.

4.8 Undesirable effects

Side effects include those common to all anti-neoplastic agents: gastrointestinal disturbances, headache, allergic reactions, fever, weakness, alopecia, stomatitis.

Local Adverse reactions

Two kinds of local adverse reactions are reported:

- Extravasation with risk of tissue necrosis: the infusion must be stopped, a maximum of infiltrated product aspirated and a cold dressing applied. A corticosteroid may possibly be injected or dimethyl sulfoxide applied topically. Daily surveillance is required. Indwelling i.v catheters and Portacath devices reduce the risk of extravasation.

- Recall of skin reaction due to prior radiotherapy, consisting of pain and erythema which may last several days.

Cardiotoxicity

Acute toxicity:

- Onset within 48 hours

- ECG modification may occur: arrhythmias, in particular prolonged QT interval usually with no clinical signs. In the event of arrhythmia, treatment can be continued but any associated electrolyte imbalance (hypokalemia, hyponatremia, etc.) must be corrected.

- Early onset of acute myopericarditis is rare.

Chronic toxicity

- Cardiomyopathy which may progress to congestive heart failure; this potentially fatal condition requires specialized care.

- Chronic toxicity is correlated to the total cumulative dose administered.

Prevention

Cardiotoxicity may be prevented by:

- Clinical monitoring

- Regular monitoring of cardiac function by evaluating ventricular performance using echocardiography or radionuclide scanning. These tests should be performed before the first administration and repeated regularly. Treatment should be discontinued if any significant change occurs.

- Some cardioprotective drugs can limit risks of toxicity.

Gastrointestinal disorders

Frequency not known: colitis, including neutropenic enterocolitis (typhlitis), enterocolitis.

Blood and lymphatic system disorders

Very common: Bone marrow failure.

Bone marrow depression (very common): in every patient bone marrow function will be depressed by treatment with daunorubicin and in a variable proportion of cases, severe aplasia will develop. Risk of sepsis, severe opportunistic infections may occur with bone marrow depression.

Frequency not known: febrile neutropenia, including with fatal outcomes, has been reported.

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.

Infections and Infestations

Very common: serious infections (including sepsis, septic shock and pneumonia), which sometimes can be fatal.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Frequency not known: secondary malignancies, including leukaemia have been reported in association with daunorubicin when used in combination with other antineoplastic treatments known to be associated with secondary malignancies.

Metabolism and nutrition disorders

Frequency not known: Tumour lysis syndrome.

Nervous system disorders

Frequency not known: Posterior Reversible Encephalopathy Syndrome (PRES, also known as Reversible Posterior Leukoencephalopathy Syndrome, RPLS), including with fatal outcomes, has been reported.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

In the event of overdose, all the adverse reactions may be exacerbated. Blood and bone marrow counts should be performed regularly and cardiological, radiological, and ultrasound investigations carried out to define appropriate symptomatic treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cerubidin is an anthracycline glycoside antibiotic and is a potent antileukaemia agent. It also has immunosuppressant effects.

The exact mechanism of the antineoplastic action of daunorubicin is uncertain but may involve binding to DNA and RNA 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 Acute Myelogenous Leukaemia and Acute Lymphocytic Leukaemia, 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.

5.2 Pharmacokinetic properties

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 the drug and its metabolites from the tissues is slow ($T_{1/2} = 55$ hours). Daunorubicin is rapidly metabolised in the liver. The major metabolite, daunorubicinol is also active. Daunorubicin 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.

5.3 Preclinical safety data

None.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D-Mannitol

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. The reconstituted product is incompatible with heparin sodium injection and dexamethasone sodium phosphate injection.

6.3 Shelf life

3 years.
The product after first opening and reconstitution of the powder should be used within 24 hours (see 6.4 for storage details). Once the reconstituted solution has been diluted in the infusion medium, it should be used immediately.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container. If prepared aseptically, the reconstituted solution may be stored for up to 24 hours in a refrigerator at 2 – 8°C protected from light. The reconstituted solution further diluted in infusion medium should be used immediately.

6.5 Nature and contents of container

Uncoloured Type III (Ph. Eur.) neutral glass vial fitted with butyl rubber stopper and aluminium overseal. The vials are available in packs of 1 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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 1 mg per ml. Once diluted the infusion should be given immediately. The solution should be infused 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, cerubidin may be added to a mini bag 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 be 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 recommended for dealing with major spillages.

Waste should be disposed of carefully in suitable separate containers, clearly labelled as to their contents (it should be noted that the patient's body fluids and excreta will contain appreciable amounts of antineoplastic agents and they should be treated as hazardous waste). All staff exposed to cerubidin should be recorded and monitored. Pregnant staff should not handle cerubidin.

Spill or Leaks Procedures

Daunorubicin infusion may be neutralised with sodium hypochlorite prior to disposal of unused drug or if vial is accidentally broken. The neutralised drug can be disposed of in the sink.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
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8 MARKETING AUTHORISATION NUMBER

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Page 6 of 7

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 April 1995

Date of last renewal: 20 April 2010

10 DATE OF REVISION OF THE TEXT

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