DAUNOTEC Injection (Daunorubicin)

Composition

DAUNOTEC
Each vial contains:
Daunorubicin Hydrochloride USP equivalent to Daunorubicin........ 20 mg
As a sterile, freeze-dried powder for dilution with
Sodium Chloride injection IP ..............................................................10 mL

Black Box Warning

1. DAUNOTEC after adequate reconstitution and dilution, must be given into a rapidly flowing intravenous (IV) infusion. It must never be given by the intramuscular or subcutaneous route. Severe local tissue necrosis will occur if there is extravasation during administration.
2. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure (CHF) may occur either during therapy or months to years after termination of therapy. The incidence of myocardial toxicity increases after a total cumulative dose exceeding 400 to 550 mg/m2 in adults, 300 mg/m2 in children more than 2 years of age, or 10 mg/kg in children less than 2 years of age.
3. Severe myelosuppression occurs when used in therapeutic doses; this may lead to infection or haemorrhage.
4. It is recommended that daunorubicin be administered only by physicians who are experienced in leukaemia chemotherapy and in facilities with laboratory and supportive resources adequate to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The physician and the institution must be capable of responding rapidly and completely to severe haemorrhagic conditions and/or overwhelming infection.
5. Dosage should be reduced in patients with impaired hepatic or renal function.

Dosage Form

Vial containing sterile powder for IV administration after reconstitution with Water for Injection and dilution with 0.9% Sodium Chloride injection

Pharmacology

Pharmacodynamics

Daunorubicin hydrochloride is the hydrochloride salt of an anthracycline cytotoxic antibiotic, which is an antineoplastic and a potent anti-leukaemic agent. It also has immunosuppressant effects. The exact mechanism of antineoplastic action 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. It inhibits topoisomerase II activity by stabilising the DNA-topoisomerase II complex, preventing the religation portion of the ligation-religation reaction that topoisomerase II catalyses. Single strand and double strand DNA breaks result. Daunorubicin hydrochloride may also inhibit polymerase activity, affect regulation of gene expression, and produce free radical damage to DNA. Daunorubicin hydrochloride possesses an antitumour effect against a wide spectrum of animal
Absorption
Daunorubicin is not absorbed by the gastrointestinal tract. Since the drug is extremely irritating to tissues, it has to be administered by the IV route; under these conditions the absorption is expected to be complete (i.e. if no extravasation occurs).

Distribution
Daunorubicin is rapidly and widely distributed in tissues, especially by the spleen, kidneys, liver, lungs and heart. It does not cross the blood-brain barrier, but the drug apparently crosses the placenta. The drug binds to many cellular components, particularly nucleic acids. Subsequent release of drug and its metabolites from the tissues is slow (t½ = 55 hours).

Metabolism
The drug undergoes rapid and extensive metabolism in the liver and other tissues, mainly by cytoplasmic aido-ketoreductases, producing daunorubicinol, the major metabolite, which has anti-neoplastic activity. Approximately 40% of the drug in the plasma is present as daunorubicinol within 30 minutes, and 60% in 4 hours after a dose of daunorubicin. Further metabolism via reduction cleavage of the glycosidic bond, 4-O demethylation, and conjugation with both sulphate and glucuronide have been demonstrated. Simple glycosidic cleavage of daunorubicin or daunorubicinol is not a significant metabolic pathway in humans.

Excretion
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.

Special Populations

Geriatric: Although appropriate studies with daunorubicin hydrochloride have not been performed in the geriatric population, cardiotoxicity may be more frequent in the elderly. Caution should also be used in patients who have inadequate bone marrow reserves due to old age. In addition, elderly patients are more likely to have age-related renal function impairment, which may require reduction of dosage in patients.

Paediatric: Although appropriate studies with daunorubicin hydrochloride have not been performed in the paediatric population, cardiotoxicity may be more frequent and occur at lower cumulative doses in children.

Renal Impairment: Doses of daunorubicin hydrochloride should be reduced in patients with renal impairment. Patients with serum creatinine concentrations of greater than 3 mg/dL should receive 50% of the usual daily dose.

Hepatic Impairment: Doses of daunorubicin hydrochloride should be reduced in patients with hepatic impairment. Patients with serum bilirubin concentrations of 1.2 to 3 mg/dL should receive 75% of the usual daily dose and patients with serum bilirubin concentrations greater than 3 mg/dL should receive 50% of the usual daily dose.

Indications

DAUNOTEC is indicated in
- inducing remissions of acute myelogenous and lymphocytic leukaemia; and,
- treatment of acute lymphocytic leukaemia and acute myeloid leukaemia in children, as part of a combination regimen.

Dosage And Administration
Adults

40 - 60 mg/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 45 mg/m$^2$.

*Acute Lymphocytic Leukaemia:* The recommended dose is 45 mg/m$^2$.

Paediatric

Daunorubicin dosage for children (over 2 years of age) 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 of age, the maximal cumulative dose is 300 mg/m$^2$.

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

Geriatric

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.

Hepatic and Renal Impairment

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 of 105 - 265 μmol/l. A 50% reduction is recommended in cases with serum bilirubin concentrations of above 50 μmol/l or creatinine of above 265 μmol/l.

Daunorubicin is extremely irritating to tissues and may only be administered intravenously after appropriate reconstitution and dilution (see STORAGE AND HANDLING INSTRUCTIONS). 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 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 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.

Contraindications

DAUNOTEC 20 is contraindicated in patients with

- Hypersensitivity to daunorubicin or any of the excipients, other anthracyclines or anthracenediones
- Recently exposed to, or with existing, chickenpox or herpes zoster
- Persistent myelosuppression
- Presence of severe infections
- Severe hepatic or renal function impairment
- Myocardial insufficiency
- Recent myocardial infarction
- Severe arrhythmias

Do not administer by the intramuscular route.
Daunorubicin hydrochloride must not be used if the cumulative highest dose of daunorubicin hydrochloride (500–600 mg/m² in adults, 300 mg/m² in children aged ≥2 years of age, 10 mg/kg body weight in children aged <2 years of age) or another cardiotoxic anthracycline has already been previously administered as, otherwise, the danger of life-threatening cardiac damage markedly increases.

**Warnings And Precautions**

**Drug Interactions**

DAUNOTEC is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to myelosuppression and gastrointestinal effects. The concurrent use of DAUNOTEC in combination chemotherapy with other potentially cardiotoxic drugs, or a radiation therapy of the mediastinum, increases the cardiotoxicity of daunorubicin hydrochloride. Therefore, as with the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), an especially careful supervision of the heart function during the entire therapy is required.

If patients were/are (pre)treated with medicinal products influencing the bone marrow function (e.g. cytostatics, sulphonamides, chloramphenicol, diphenylhydantoin, amidopyrine derivatives, antiretroviral agents) the possibility of a marked disorder of haemopoiesis should be borne in mind. The dose of DAUNOTEC should be modified if required. If combined with other cytostatics (e.g. cytarabine, cyclophosphamide), the toxic effects of daunorubicin hydrochloride therapy may be potentiated.

Daunorubicin hydrochloride is mainly metabolised in the liver; each accompanying medication influencing liver function may also influence the metabolism or pharmacokinetics of DAUNOTEC and, as a consequence, influence efficacy and/or toxicity.

The combination of DAUNOTEC with potentially hepatotoxic medicinal products (e.g. methotrexate) may, upon impairment of the hepatic metabolism and/or biliary excretion of daunorubicin hydrochloride, lead to an increase in toxicity of the substance. This may result in a potentiation of the side effects.

Upon concurrent administration of other cytostatics, the risk for the incidence of gastrointestinal side effects increases. Medicinal products leading to a delayed excretion of uric acid (e.g. sulphonamides, certain diuretics) may cause potentiated hyperuricaemia upon concurrent use of DAUNOTEC.

It should generally be taken into consideration that the intake and absorption of oral accompanying medicinal products may be considerably influenced by an oral and gastrointestinal mucositis frequently occurring in association with an intensive daunorubicin hydrochloride-containing chemotherapy.

In association with the concurrent intake of thrombocyte aggregation-inhibiting substances (e.g. acetylsalicylic acid), an additionally increased bleeding tendency must be anticipated in thrombocytopaenic patients.

No vaccinations with viable pathogens should be carried out during daunorubicin hydrochloride therapy.

**General**

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

Relative contraindications are high-grade pancytopaenia or isolated leuco-/thrombo-cytopaenia.

Further relative contraindications are severe cardiac arrhythmias, in particular, ventricular tachycardias or arrhythmias with clinically relevant haemodynamic effects and clinically manifest heart failure – even in the history, myocardial infarction, severe disorders of the kidneys and liver, pregnancy and a poor general condition of the patient. The treating physician should weigh the benefits and risks and decide, in each individual case, on the treatment.

Uncontrolled infections, especially viral diseases (Herpes zoster) can develop into life-threatening exacerbations after
Daunorubicin hydrochloride administration because of its immunosuppressive effect. Special caution should be exercised in patients with preceding, concurrent or planned radiotherapy. These patients have an increased risk of local reactions in the radiation area (recall phenomena) during treatment with DAUNOTEC. A preceding radiation of the mediastinum increases the cardiotoxicity of DAUNOTEC.

Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropaenia, thrombocytopaenia, and generalised infections) before beginning treatment with daunorubicin.

Haematopoietic System

After administration of a therapeutic dose, myelosuppression will occur in all patients. Reversible bone marrow suppression develops dose-dependently and consists primarily of leukopaenia, granulocytopaenia (neutropaenia) and thrombocytopaenia. Anaemia occurs more rarely. The nadir is achieved 8 to 10 days after starting therapy. Recovery generally occurs 2 to 3 weeks after the last injection. To avoid myelotoxic complications, careful monitoring of the blood count before and during treatment with special attention to the leukocytes, granulocytes, platelets and erythrocytes is necessary. Fever, infections, sepsis, septic shock, haemorrhages and tissue hypoxia may occur as sequelae of the myelosuppression and these may even lead to death. It must be guaranteed that a severe infection and/or bleeding episode can be treated quickly and effectively. Myelosuppression may require intensive supportive treatment.

Secondary Leukaemia

Secondary leukaemia, with or without a pre-leukaemic phase, has been reported in patients treated with anthracyclines, including daunorubicin. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, in combination with radiotherapy, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukaemias can have a 1- to 3-year latency period.

Cardiotoxicity

Damage to the myocardium is one of the major risks of treatment with DAUNOTEC. Toxic myocardial damage by daunorubicin hydrochloride can occur in two forms. The dose-independent ‘acute type’ is manifested by supraventricular arrhythmias (sinus tachycardia, premature ventricular contractions, AV-block) and/or non-specific ECG abnormalities (ST-T wave changes, low voltage QRS complex, T waves). Angina pectoris, myocardial infarction, endomyocardial fibrosis, pericarditis/myocarditis have also been reported. In the ‘delayed type’, congestive cardiomyopathy may develop, especially after high cumulative doses of daunorubicin hydrochloride. Sometimes this occurs during therapy, but frequently also only months to years after completing treatment and is clinically manifested by global heart failure, which occasionally leads to death through acute heart failure. The severity and frequency of these side effects depend on the cumulative daunorubicin hydrochloride dose. Careful monitoring of the cardiac function before, during and after treatment is, therefore, recommended in order, to identify the risk of cardiac complications as early as possible. For routine monitoring the most suitable means are ECG and the determination of the left ventricular ejection fraction (UGC, MUGA scan).

The threshold dose for adults is about 550 mg/m², for children over two years of age about 300 mg/m² and for children under 2 years about 10 mg/kg body weight.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g. trastuzumab). Anthracyclines, including DAUNOTEC should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing
cardiotoxicity. Under these conditions, a total cumulative dose of 400 mg/m\(^2\) in adults should be exceeded only with extreme caution. Elderly patients and patients with a history of cardiac disease or manifest arterial hypertension and thoracic irradiation are endangered to a greater degree, as are also children. Under these conditions, a total cumulative dose of 400 mg/m\(^2\) should not be exceeded in adults. Because of an increased risk of myocardial damage in children and adolescents, long-term cardiologic follow-up observation is recommended in these cases.

Several long-term studies in children also suggest that after anthracycline treatment, congestive cardiomyopathies with a latency of many years and a progradent course may occur. In comparison to adults, already lower cumulative total doses in children probably lead to clinically relevant cardiac dysfunction. A publication by Steinherz et al. (JAMA, Sep 25, 1991 – Vol 266, No. 12) describes the cardiotoxic long-term side effects of doxorubicin and daunorubicin hydrochloride in 201 treated children. The patients received a cumulative total dose of doxorubicin and/or daunorubicin hydrochloride between 200 and 1,275 mg/m\(^2\) (median 450 mg/m\(^2\)), partly also through mediastinal radiation. Treatments took place 4 to 20 years ago (median, 7 years). The cardiotoxicity of doxorubicin was assumed to be comparable to that of daunorubicin hydrochloride. Impaired cardiac pumping function was seen if the shortening fraction in the echocardiogram was determined to be <29% or the ejection fraction in the radionuclide ventriculogram was <50% or a decrease was observed upon physical exercise. The incidence of impaired cardiac function was 11% when the cumulative anthracycline dose was below 400 mg/m\(^2\), 28% at a dose between 400 and 599 mg/m\(^2\), 47% at a dose between 600 and 799 mg/m\(^2\), and 100% in seven patients who had received more than 800 mg/m\(^2\). Additional radiation increased the incidence of cardiac dysfunction at each dose stage. Out of 201 examined patients, 9 additionally experienced cardiac symptoms in the form of cardiac insufficiency, conduction disorders and arrhythmias. In 4 out of the 9 patients affected, symptoms occurred for the first time at 12 to 18 years after completion of chemotherapy.

### Imnosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including daunorubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving daunorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

### Gastrointestinal

Daunorubicin may cause nausea and vomiting. Severe nausea and vomiting may produce dehydration. Nausea and vomiting may be prevented or alleviated by the administration of appropriate antiemetic therapy. Mucositis/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy. Cases of colitis, enterocolitis and neutropaenic enterocolitis (typhlitis) have been observed in patients treated with daunorubicin. Treatment discontinuation and prompt appropriate medical treatment are recommended.

### General Disorders and Administration Site Conditions

After paravasal administration local irritation and, depending on the quantity involved, severe cellulitis, painful ulceration and tissue necrosis will occur. Under some circumstances, they may require surgical intervention. Irreversible tissue damage is possible. Local phlebitis, thrombophlebitis and/or venous clerosis/phlebosclerosis may also occur, especially if DAUNOTEC is injected into small vessels or repeatedly into the same vein. The risk of phlebitis/thrombophlebitis can be minimised by following the procedures recommended in DOSAGE AND ADMINISTRATION.
Skin and Subcutaneous Tissue Disorders

Complete alopecia involving beard growth and the scalp, axillary and pubic hair occurs almost always with full doses of daunorubicin. This side effect may cause distress to patients but is usually reversible, with regrowth of hair, which usually occurs within 2–3 months from the termination of therapy.

Reproductive System and Breast Disorders

Daunorubicin hydrochloride inhibits fertility. Amenorrhoea and azoospermia may occur. The severity is dose-dependent. Irreversible disorders of fertility are possible.

Care should be taken to avoid extravasation during IV administration. All steps should be taken to avoid tissue damage and bandages should be avoided. Facial flushing or erythematous streaking along veins 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 affected 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 change, 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.

Infections and Infestations

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 DAUNOTEC which might depress the bone marrow to the point where anti-infective agents would no longer be effective. If during DAUNOTEC treatment a patient becomes febrile (regardless of the neutrophil count), treatment with broad-spectrum antibiotics should be initiated. 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.

Impaired Fertility

Daunorubicin could induce chromosomal damage in human spermatozoa. Men should receive counselling on sperm conservation before start of DAUNOTEC treatment because of the possibility of irreversible infertility.

Men undergoing treatment with DAUNOTEC should use effective contraceptive methods during and up to 6 months after treatment.

Women of childbearing potential have to use effective contraception during treatment with DAUNOTEC. For women who want to become pregnant after completing DAUNOTEC treatment, genetic counselling is also recommended.

Effects on the Ability to Drive and Use Machines

There have been no reports explicitly relating to the effects of daunorubicin treatment on the ability to drive or use machines.

Renal Impairment

Renal impairment can also induce an increase in toxicity. The renal function should therefore be monitored before starting treatment.

DAUNOTEC 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 DAUNOTEC should be limited to 400 mg/m\(^2\) when radiation therapy to the mediastinum has been previously administered. The dose of DAUNOTEC should not be repeated in the presence of bone marrow depression or buccal ulceration.

Hyperuricaemia and uric acid nephropathy may occur as a consequence of massive death of the leukaemic cells, with possible impairment of renal function, especially in the presence of elevated pre-treatment white blood cell (WBC) counts. The extent is dependent on the total tumour mass. Hence prophylactic administration of allopurinol is necessary in the treatment of acute leukaemia (first cycle) in order to avoid tubulus damage with renal failure for the above reasons. The development of a nephrotic syndrome may be induced. Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimise potential complications of tumour-lysis syndrome.

### Hepatic Impairment

Daunorubicin hydrochloride is metabolised predominantly in the liver and is excreted via the bile. To avoid complications, monitoring of the liver function before starting treatment with DAUNOTEC is recommended. Impairment of liver function requires a dose reduction, which is based on the serum bilirubin level.

### Pregnancy

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

Studies in animals have shown reproductive toxicity. Like most other anticancer drugs, daunorubicin has shown embryotoxic, teratogenic, mutagenic and carcinogenic potential in animals. There are no or limited amount of data regarding the use of daunorubicin in pregnant women, although a few women who received daunorubicin during the second and third trimesters of pregnancy have delivered apparently normal infants.

According to experimental data, the drug must be considered as a potential cause of foetal malformations when administered to a pregnant woman. Daunorubicin should not be used during pregnancy unless the clinical condition of the woman requires treatment with daunorubicin and justifies the potential risk to the foetus. Women of childbearing potential who have to undergo daunorubicin therapy should be apprised of the potential hazard to the foetus and should be advised to avoid becoming pregnant during treatment. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the woman should be informed of the potential hazard to the foetus. The possibility of genetic counselling should also be utilised. In any case, cardiologic examination and a blood count are recommended in foetuses and newborns born to mothers who received treatment with daunorubicin during pregnancy.

### Lactation

It is not known whether daunorubicin/metabolites are excreted in human milk; other anthracyclines are excreted in human milk. DAUNOTEC is contraindicated during breastfeeding.

### Paediatric Use

Although appropriate studies with daunorubicin hydrochloride have not been performed in the paediatric population, cardiotoxicity may be more frequent and occur at lower cumulative doses in children.

### Geriatric Use

Although appropriate studies with daunorubicin hydrochloride have not been performed in the geriatric population, cardiotoxicity may be more frequent in the elderly. Caution should also be used in patients who have inadequate bone marrow reserves due to old age. In addition, elderly patients are more likely to have age-related renal function
impairment, which may require reduction of dosage in patients receiving daunorubicin hydrochloride.

### Undesirable Effects

<table>
<thead>
<tr>
<th>Category</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Bone marrow failure, anaemia, granulocytopenia (neutropaenia), leucopaenia, thrombocytopenia.</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Serious infections (including sepsis, septic shock, and pneumonia), which sometimes can be fatal</td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td>Anaphylaxis and anaphylactoid reactions</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Dehydration, tumour-lysis syndrome, acute hyperuricaemia</td>
</tr>
<tr>
<td><strong>Neoplasms Benign, Malignant and Unspecified</strong></td>
<td>Secondary leukaemia has been reported in association with daunorubicin when used in combination with other antineoplastics</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Cardiomyopathy (clinically manifested by dyspnoea, cyanosis, dependent oedema, hepatomegaly, ascites, pleural effusion and overt congestive heart failure), endomyocardial fibrosis, myocardial ischaemia (angina) and myocardial infarction, pericarditis/myocarditis, supraventricular tachyarrhythmias (such as sinus tachycardia, premature ventricular contractions, heart block)</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Flashes, haemorrhage, shock</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>Tissue hypoxia</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Abdominal pain, diarrhoea, oesophagitis, mucositis/stomatitis (pain or burning sensation, erythema, erosions-ulcerations, bleeding, infections), diarrhoea, nausea vomiting, colitis, including neutropaenic enterocolitis (typhlitis), enterocolitis</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Alopecia (reversible), contact dermatitis, erythema, hypersensitivity to irradiated skin (‘radiation recall reaction’), pruritus, skin rash, skin and nail hyperpigmentation, urticaria.</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td>Nephrotic syndrome, uric acid nephropathy, red colour of urine for 1–2 days after administration</td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td>Amenorrhoea, azoospermia</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
</tr>
</tbody>
</table>
Chills, fever, pain, death, fulminant hyperpyrexia, perivenous extravasation (immediate local pain/burning sensation, severe cellulitis, painful ulceration, and tissue necrosis), venous sclerosis/phlebosclerosis, thrombophlebitis, local phlebitis

**Investigations**

ECG abnormalities (such as non-specific ST-T wave changes, low-voltage QRS complex, T-waves), transient elevations in serum bilirubin, aspartate aminotransferase (AST) and alkaline phosphatase concentrations

**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. Leucopaenia is usually more significant than thrombocytopenia. The nadir for leucopaenia usually occurs between 10 and 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 treatment, by isolating the patient from infection during 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.

Rapid destruction of a large number of leukaemia cells may cause a rise in 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.

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, swelling of the feet and lower limbs, or by minor changes in the ECG and, for this reason, an ECG examination should be made at regular intervals during the treatment. Cardiotoxicity usually appears within 1–6 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 CHF increases significantly when the total cumulative dosage exceeds 600 mg/m² in adults, 300 mg/m² in children ≥2 years, or 10 mg/kg in children <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.

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 18002677779 (Cipla Number) or you can report to PvPI on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

**Overdosage**

**Overdosage and Intoxication**

Very high single doses of daunorubicin may cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10–14 days. The occurrence of cardiac damage up to several months after an overdose has been reported for anthracyclines.

**Treatment of Intoxication**

A specific antidote for daunorubicin hydrochloride is not known. In case of myocardial weakness, a cardiologist should be consulted and treatment with daunorubicin hydrochloride withdrawn. In the presence of marked myelosuppression, suitable supportive treatment should be initiated, depending on which myelopoietic system is mostly affected, e.g. the...
transfer of the patient to an aseptic room or transfusion of the lacking cell elements.

---

**Extravasation**

Paravenous injection leads to local necrosis and thrombophlebitis. Should a burning sensation develop in the region of the infusion needle, this indicates paravenous administration.

---

**Treatment of Extravasation**

If extravasation occurs, the infusion or injection should be stopped immediately. The needle should initially be left in place and then removed after brief aspiration. It is recommended that dimethyl sulphoxide 99% (DMSO 99%) should be applied locally to an area twice as large as the area affected (four drops for a 10 cm² skin surface) and that this should be repeated three times daily over a period of at least 14 days. If necessary, debridement should also be considered. Because of the contradictory mechanism, cooling of the area, e.g. to reduce pain, should take place sequentially with the DMSO application (vasoconstriction versus vasodilatation). Other measures given in literature are disputed and are not of unequivocal value.

---

**Incompatibility**

The reconstitution is incompatible with heparin sodium injection and dexamethasone sodium phosphate.

---

**Storage And Handling Instructions**

Store below 25°C and protect from light.

After reconstitution DAUNOTEC should be stored at 2°C to 8°C, protected from light. Keep out of the reach of children.

---

**Special Precautions for Disposal**

Discard the solution if the contents are not clear or if particulate matter or discolouration is observed.

---

**Preparation of the Solution**

The contents of the vial should be reconstituted with 4 mL of Sterile Water for Injection and agitated gently until the material has completely dissolved. The sterile vial contents provide 20 mg of daunorubicin, with 5 mg of daunorubicin per mL. The desired dose is withdrawn into a syringe containing 10 to 15 mL of 0.9% Sodium Chloride injection and then injected over a 20-minute period into the tubing or sidearm in a rapidly flowing IV infusion of 5% Dextrose injection or 0.9% Sodium Chloride injection.

---

**Protective Measures**

The following protective measures are recommended due to the toxic nature of the compound:
Personnel should be trained in good techniques for reconstitution and handling.
Pregnant staff should be excluded from working with this drug.
Personnel handling daunorubicin should wear protective clothing: goggles, gowns, and disposable gloves and masks.
A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed, absorbent paper.
All items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk, waste-disposal bags for high-temperature incineration.
Spillage or leakage should be treated with diluted sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water.
All cleaning materials should be disposed of as indicated previously. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution; medical attention should be sought. Always wash the hands after removing the gloves. The drug should be used within 24 hours of first penetration of the rubber stopper. Discard any unused solution.

**Packaging Information**

DAUNOTEC
Available as a colourless glass vial containing 20 mg daunorubicin hydrochloride as a freeze-dried powder stoppered with a chloronbutyl rubber stopper and sealed with an aluminium cap with an inset polypropylene disk (flip-off type) together with an ampoule of reconstituting solvent containing 10 mL of sterile physiological saline solution.

_Last Updated: June 2019_
_Last Reviewed: June 2019_

**DAUNOTEC Injection**

Source URL: https://ciplamed.com/content/daunotec-injection