SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

DAUNOPLUS (Daunorubicin hydrochloride 20 mg injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains daunorubicin hydrochloride equivalent to daunorubicin.
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Lyophilized Powder for Injection

Dark red lyophilized cake

4. Clinical particulars

4.1 Therapeutic indications

Daunorubicin hydrochloride in combination with other approved anticancer drugs is indicated for remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) of adults and for remission induction in acute lymphocytic leukemia of children and adults.

4.2 Posology and method of administration

Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit.

Principles

In order to eradicate the leukemic cells and induce a complete remission, a profound suppression of the bone marrow is usually required. Evaluation of both the peripheral blood and bone marrow is mandatory in the formulation of appropriate treatment plans.

It is recommended that the dosage of daunorubicin hydrochloride be reduced in instances of hepatic or renal impairment. For example, using serum bilirubin and serum creatinine as indicators of liver and kidney function, the following dose modifications are recommended:

Serum Bilirubin	Serum Creatinine	Dose Reduction
1.2 to 3 mg%	-	25%
>3 mg%	-	50%
-	>3 mg%	50%

Representative Dose Schedules and Combination for the Approved Indication of Remission

Induction in Adult Acute Nonlymphocytic Leukemia

In Combination

For patients under age 60, daunorubicin hydrochloride 45 mg/m /day IV on days 1, 2, and 3 of the first course and on days 1, 2 of subsequent courses AND cytosine arabinoside 100 mg/m /day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses.

For patients 60 years of age and above, daunorubicin hydrochloride 30 mg/m^2/day IV on days 1, 2, and 3 of the first course and on days 1, 2 of subsequent courses AND cytosine arabinoside 100 mg/m^2/day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses. This daunorubicin hydrochloride dose-reduction is based on a single study and may not be appropriate if optimal supportive care is available.

The attainment of a normal-appearing bone marrow may require up to three courses of induction therapy. Evaluation of the bone marrow following recovery from the previous course of induction therapy determines whether a further course of induction treatment is required.

Representative Dose Schedule and Combination for the Approved Indication of Remission Induction in Pediatric Acute Lymphocytic Leukemia

In Combination

Daunorubicin hydrochloride 25 mg/m^2 IV on day 1 every week, vincristine 1.5 mg/m^2IV on day 1 every week, prednisone 40 mg/m^2 PO daily. Generally, a complete remission will be obtained within four such courses of therapy; however, if after four courses the patient is in partial remission, an additional one or, if necessary, two courses may be given in an effort to obtain a complete remission.

In children less than 2 years of age or below 0.5 m^2 body surface area, it has been recommended that the daunorubicin hydrochloride dosage calculation should be based on weight (1 mg/kg) instead of body surface area.

Representative Dose Schedules and Combination for the Approved Indication of Remission Induction in Adult Acute Lymphocytic Leukemia

In Combination

Daunorubicin hydrochloride 45 mg/m^2/day IV on days 1, 2, and 3 AND vincristine 2 mg^{2}IV on days 1, 8, and 15; prednisone 40 mg/m^2/day PO on days 1 through 22, then tapered between days 22 to 29; Lasparaginase 500 IU/kg/day x 10 days IV on days 22 through 32.

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 mL to 15 mL of 0.9% Sodium Chloride Injection, USP and then injected into the tubing or sidearm in a rapidly flowing IV infusion of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP. Daunorubicin hydrochloride should not be administered mixed with other drugs or heparin.

Renal and Hepatic Impairment

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

4.3 Contraindications

- hypersensitivity to daunorubicin or any other component of the product, other anthracyclines, or anthracenediones;
- persistent myelosuppression;
- presence of severe infections;
- severe hepatic (Child-Pugh Grade C [total score 10-15]) or renal function impairment (GFR <10 mL/min or serum creatinine >7.9 mg/dL);
- myocardial insufficiency;
- recent myocardial infarction;
- severe arrhythmias;
- previous treatments with maximum cumulative doses of daunorubicin, other anthracyclines and/or anthracenediones.

4.4 Special warnings and precautions for use

WARNINGS

- Daunorubicin Hydrochloride Injection must be given into a rapidly flowing intravenous infusion. It must never be given by the intramuscular or subcutaneous route. Severe local tissue necrosis will occur if there is extravasation during administration.
- Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure 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/m in adults, 300 mg/m in children more than 2 years of age, or 10 mg/kg in children less than 2 years of age.
- Severe myelosuppression occurs when used in therapeutic doses; this may lead to infection or hemorrhage.
- It is recommended that daunorubicin hydrochloride be administered only by physicians who are experienced in leukemia 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 institution must be capable of responding rapidly and completely to severe hemorrhagic conditions and/or overwhelming infection.
- Dosage should be reduced in patients with impaired hepatic or renal function.

Bone Marrow

Daunorubicin hydrochloride is a potent bone marrow suppressant. Suppression will occur in all patients given a therapeutic dose of this drug. Therapy with daunorubicin hydrochloride should not be started in patients with pre-existing drug-induced bone marrow suppression unless the benefit from such treatment warrants the risk. Persistent, severe myelosuppression may result in superinfection or hemorrhage.

Cardiac Effects

Special attention must be given to the potential cardiac toxicity of daunorubicin hydrochloride, particularly in infants and children. Pre-existing heart disease and previous therapy with doxorubicin are co-factors of increased risk of daunorubicin-induced cardiac toxicity and the

benefit-to-risk ratio of daunorubicin hydrochloride therapy in such patients should be weighed before starting daunorubicin hydrochloride. In adults, at total cumulative doses less than 550 mg/m^2, acute congestive heart failure is seldom encountered. However, rare instances of pericarditis-myocarditis, not dose-related, have been reported.

In adults, at cumulative doses exceeding 550 mg/m^2, there is an increased incidence of drug-induced congestive heart failure. Based on prior clinical experience with doxorubicin, this limit appears lower, namely 400 mg/m^2, in patients who received radiation therapy that encompassed the heart. In infants and children, there appears to be a greater susceptibility to anthracycline-induced cardiotoxicity compared to that in adults, which is more clearly dose-related. Anthracycline therapy (including daunorubicin) in pediatric patients has been reported to produce impaired left ventricular systolic performance, reduced contractility, congestive heart failure or death. These conditions may occur months to years following cessation of chemotherapy. This appears to be dose-dependent and aggravated by thoracic irradiation. Long-term periodic evaluation of cardiac function in such patients should, thus, be performed. In both children and adults, the total dose of daunorubicin hydrochloride administered should also take into account any previous or concomitant therapy with other potentially cardiotoxic agents or related compounds such as doxorubicin.

There is no absolutely reliable method of predicting the patients in whom acute congestive heart failure will develop as a result of the cardiac toxic effect of daunorubicin hydrochloride. However, certain changes in the electrocardiogram and a decrease in the systolic ejection fraction from pre-treatment baseline may help to recognize those patients at greatest risk to develop congestive heart failure. On the basis of the electrocardiogram, a decrease equal to or greater than 30% in limb lead QRS voltage has been associated with a significant risk of drug-induced cardiomyopathy. Therefore, an electrocardiogram and/or determination of systolic ejection fraction should be performed before each course of daunorubicin hydrochloride. In the event that one or the other of these predictive parameters should occur, the benefit of continued therapy must be weighed against the risk of producing cardiac damage.

Early clinical diagnosis of drug-induced congestive heart failure appears to be essential for successful treatment.

Evaluation of Hepatic and Renal Function

Significant hepatic or renal impairment can enhance the toxicity of the recommended doses of daunorubicin hydrochloride; therefore, prior to administration, evaluation of hepatic function and renal function using conventional clinical laboratory tests is recommended.

Pregnancy

Daunorubicin hydrochloride may cause fetal harm when administered to a pregnant woman. An increased incidence of fetal abnormalities (parieto-occipital cranioschisis, umbilical hernias, or rachischisis) and abortions was reported in rabbits at doses of 0.05 mg/kg/day or approximately $1/100^{th}$ of the highest recommended human dose on a body surface area basis. Rats showed an increased incidence of esophageal, cardiovascular and urogenital abnormalities as well as rib fusions at doses of 4 mg/kg/day or approximately 1/2 the human dose on a body surface area basis. Decreases in fetal birth weight and post-delivery growth rate were observed in mice. There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Women of childbearing potential should be advised to avoid becoming pregnant.

Secondary Leukemias

There have been reports of secondary leukemias in patients exposed to topoisomerase II inhibitors when used in combination with other antineoplastic agents or radiation therapy.

Extravasation at Injection Site

Extravasation of daunorubicin hydrochloride at the site of intravenous administration can cause severe local tissue necrosis.

PRECAUTIONS

General

Therapy with daunorubicin hydrochloride requires close patient observation and frequent complete blood-count determinations. Cardiac, renal, and hepatic function should be evaluated prior to each course of treatment.

Appropriate measures must be taken to control any systemic infection before beginning therapy with daunorubicin hydrochloride.

Daunorubicin hydrochloride may transiently impart a red coloration to the urine after administration, and patients should be advised to expect this.

Laboratory Tests

Daunorubicin hydrochloride may induce hyperuricemia secondary to rapid lysis of leukemic cells. As a precaution, allopurinol administration is usually begun prior to initiating antileukemic therapy. Blood uric acid levels should be monitored and appropriate therapy initiated in the event that hyperuricemia develops.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Daunorubicin hydrochloride, when injected subcutaneously into mice, causes fibrosarcomas to develop at the injection site. When administered to mice thrice weekly intraperitoneally, no carcinogenic effect was noted after 18 months of observation. In male rats administered daunorubicin thrice weekly for 6 months, at $1/70^{th}$ the recommended human dose on a body surface area basis, peritoneal sarcomas were found at 18 months. A single IV dose of daunorubicin administered to rats at 1.6 fold the recommended human dose on a body surface area basis caused mammary adenocarcinomas to appear at 1 year.

Daunorubicin was mutagenic *in vitro* (Ames assay, V79 hamster cell assay), and clastogenic *in vitro* (CCRFCEM human lymphoblasts) and *in vivo* (SCE assay in mouse bone marrow) tests.

In male dogs at a daily dose of 0.25 mg/kg administered intravenously, testicular atrophy was noted at autopsy. Histologic examination revealed total aplasia of the spermatocyte series in the seminiferous tubules with complete aspermatogenesis.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from daunorubicin, mothers should be advised to discontinue nursing during daunorubicin therapy.

Elderly

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.

Pediatric Use

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

4.5 Interaction with other medicinal products and other forms of Interaction

Use of daunorubicin in a patient who has previously received doxorubicin increases the risk of cardiotoxicity. Daunorubicin hydrochloride should not be used in patients who have previously received the recommended maximum cumulative doses of doxorubicin or daunorubicin hydrochloride. Cyclophosphamide used concurrently with daunorubicin hydrochloride may also result in increased cardiotoxicity.

Dosage reduction of daunorubicin hydrochloride may be required when used concurrently with other myelosuppressive agents.

Hepatotoxic medications, such as high-dose methotrexate, may impair liver function and increase the risk of toxicity.

4.6 Pregnancy and lactation

Pregnancy

Daunorubicin hydrochloride may cause fetal harm when administered to a pregnant woman. An increased incidence of fetal abnormalities (parieto-occipital cranioschisis, umbilical hernias, or rachischisis) and abortions was reported in rabbits at doses of 0.05 mg/kg/day or approximately $1/100^{th}$ of the highest recommended human dose on a body surface area basis. Rats showed an increased incidence of esophageal, cardiovascular and urogenital abnormalities as well as rib fusions at doses of 4 mg/kg/day or approximately 1/2 the human dose on a body surface area basis. Decreases in fetal birth weight and post-delivery growth rate were observed in mice. There

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4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Dose-limiting toxicity includes myelosuppression and cardiotoxicity (see WARNINGS section). Other reactions include:

Cutaneous

Reversible alopecia occurs in most patients. Rash, contact dermatitis and urticaria have occurred rarely.

Gastrointestinal

Acute nausea and vomiting occur but are usually mild. Antiemetic therapy may be of some help. Mucositis may occur 3 to 7 days after administration. Diarrhea and abdominal pain have occasionally been reported.

Local

If extravasation occurs during administration, severe local tissue necrosis, severe cellulitis, thrombophlebitis, or painful induration can result.

Acute Reactions

Rarely, anaphylactoid reaction, fever, and chills can occur. Hyperuricemia may occur, especially in patients with leukemia, and serum uric acid levels should be monitored.

4.9 Overdose

Acute overdosage with daunorubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications. Very high single doses of daunorubicin may be expected to cause acute myocardial degeneration (within 24 hours) and severe myelosuppression (within 10–14 days). Treatment should aim to support the patient during this period. Delayed cardiac failures have been observed with anthracyclines up to 6 months after an overdose. Patients have to be observed carefully: if signs of cardiac failure arise, they should be treated along conventional lines.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antineoplastic Agents (Anthracyclines and related substances);
ATC code: L01DB02

Daunorubicin has antimitotic and cytotoxic activity through a number of proposed mechanisms of action. Daunorubicin forms complexes with DNA by intercalation between base pairs. It inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex, preventing the religation portion of the ligation-religation reaction that topoisomerase II catalyzes. 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 antitumor effect against a wide spectrum of animal tumors, either grafted or spontaneous.

5.2 Pharmacokinetics:

General

Following intravenous injection of Daunorubicin hydrochloride, plasma levels of daunorubicin decline rapidly, indicating rapid tissue uptake and concentration. Thereafter, plasma levels decline slowly with a half-life of 45 minutes in the initial phase and 18.5 hours in the terminal phase. By 1 hour after drug administration, the predominant plasma species is daunorubicinol, an active metabolite, which disappears with a half-life of 26.7 hours.

Distribution

Daunorubicin hydrochloride is rapidly and widely distributed in tissues, with highest levels in the spleen, kidneys, liver, lungs, and heart. The drug binds to many cellular components, particularly nucleic acids. There is no evidence that daunorubicin crosses the blood-brain barrier, but the drug apparently crosses the placenta.

Metabolism and Elimination

Daunorubicin hydrochloride is extensively metabolized in the liver and other tissues, mainly by cytoplasmic aldo-keto reductases, producing daunorubicinol, the major metabolite which has antineoplastic 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 sulfate and glucuronide have been demonstrated. Simple glycosidic cleavage of daunorubicin or daunorubicinol is not a significant metabolic pathway in man. Twenty-five percent of an administered dose of daunorubicin hydrochloride is eliminated in an active form by urinary excretion and an estimated 40% by biliary excretion.

5.3 Preclinical safety data

No Information available

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol

Sodium Hydroxide

Water for Injection

6.2 Incompatibilities

Daunorubicin has been reported to be incompatible with heparin sodium, which might cause the drug to precipitate in the solution, and with aluminum. Incompatibility has also been reported when a daunorubicin hydrochloride solution is mixed with a solution of dexamethasone sodium phosphate, aztreonam, allopurinol sodium, fludarabine, piperacillin/tazobactam and

aminophylline. Daunorubicin can be used in combination with other antitumor agents, but it is not recommended that it be mixed with other drugs in the same syringe.

6.3 Shelf life

24 Months

6.4 Special Precaution for storage

Store below 25°C in a dry place. protected from Light. Do not freeze.

6.5 Nature and contents of container

15 ml flint tubular glass vial closed with 20 mm rubber plugs and sealed with 20mm Aluminium flip off Seal is placed in a carton along with pack insert.

6.6 Special precautions for disposal and other handling

Preparation of the solution – Daunorubicin hydrochloride powder for injection should be reconstituted by adding 4 mL of sterile Water for Injection. The vial content is under a negative pressure to minimize aerosol formation during reconstitution; particular care is needed when the needle is inserted: inhalation of any aerosol produced during reconstitution must be avoided. The vial should be gently shaken until the drug is completely dissolved. The resultant solution contains 5 mg of daunorubicin per mL. The reconstituted solution should be protected from light and is stable for 24 hours at room temperature or 48 hours at 4°C - 10°C.

Intravenous administration – The required dose of the reconstituted solution has to be withdrawn into a syringe containing 10 to 15 mL of 0.9% sodium chloride and slowly injected into the tubing of a freely flowing IV infusion of 0.9% sodium chloride or 5% dextrose to minimize the risk of drug extravasation and make sure that the vein is flushed after the administration of the drug.

Protective measures – The following protective recommendations are given due to the toxic nature of the compound:

- Personnel should be trained in good technique 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 hands after removing gloves;
- The drug should be used within 24 hours of first penetration of the rubber stopper. Discard any unused solution.

7. MARKETING AUTHORIZATION HOLDER

M/S VHB MEDI SCIENCES LTD.

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8. MARKETING AUTHORIZATION NUMBER

06000/07616/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

24/05/2021

10. DATE OF REVISION OF THE TEXT

18/07/2023