DAUNOCIN for Inj.

Daunorubicin HCl

COMPOSITION
Each vial contains
Daunorubicin Hydrochloride ..... 21.4 mg
(As Daunorubicin 20 mg(Potency))

Each Diluent for Daunocin ampule contains
Water for injection ..... 4 mL.

PRODUCT DESCRIPTION
Daunocin vial : Red, freeze-dried cake in a colorless vial.
Diluent : Clear, colorless solution in a colorless ampule.

PHARMACODYNAMICS
Mechanisms of Action : Daunorubicin hydrochloride is an antineoplastic antibiotic. Although the exact mechanism(s) of action has not been fully elucidated, the drug appears to inhibit DNA synthesis and DNA—dependent RNA synthesis by forming a complex with DNA with intercalation between base pairs and uncoiling of the helix. The distortion impairs the template activity of DNA. Daunorubicin may also inhibit polymerase activity, affect regulation of gene expression, and be involved in free radical damage to DNA. Although daunorubicin is maximally cytotoxic in the S phase, the drug is not cycle - phase specific. Daunorubicin hydrochloride also has antibacterial and immunosuppressive properties.

PHARMACOKINETICS
Absorption : Daunorubicin hydrochloride is extremely irritating to tissues and, therefore, must be administered IV.
Distribution : Daunorubicin is rapidly and widely distributed in tissues, with highest levels in the spleen, kidneys, liver, lungs, and heart. The drug is absorbed by cells and binds to cellular components, particularly nucleic acids. There is no evidence that daunorubicin crosses the blood—brain barrier, but the drug apparently crosses the placenta. It is not known if daunorubicin is distributed into milk.
Elimination : Following rapid IV administration, total plasma concentrations of daunorubicin and its metabolites decline in a triphasic manner, and plasma concentrations of unchanged daunorubicin decline in a biphasic manner. The plasma half—life of daunorubicin averages 45 minutes in the initial phase and 18.5 hours in the terminal phase. By 1 hour after administration of daunorubicin, the predominant form of the drug in plasma is the metabolite daunorubicinol, which has an average terminal plasma half—life of 26.7 hours. 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. Additional metabolism by reductive cleavage of the glycosidic bond produces aglycones, which have little or no cytotoxic activity and are demethylated and conjugated with sulfate and glucuronide by microsomal enzymes. Daunorubicin and its metabolites are excreted in urine and bile. Urinary excretion of the drug and its metabolites is reported to be 14—23% of the dose, with most urinary excretion of the drug occurring within 3 days. After the first 24 hours, the drug is excreted in urine mainly as daunorubicinol. An estimated 40% of a dose is eliminated by biliary excretion.

INDICATION
Daunorubicin hydrochloride in combination with other approved anticancer drugs is indicated for :
i) Acute myeloblastic leukaemia
ii) Acute lymphoblastic leukaemia
iii) Other tumors e.g. neuroblastoma, rhabdomyosarcoma.

RECOMMANDED DOSE
Reconstitution and Administration
Daunorubicin hydrochloride is administered IV. The drug is extremely irritating to tissues and, therefore, should not be given IM or subcutaneously. Care should be taken to avoid extravasation of the drug. Daunorubicin hydrochloride powder for injection is reconstituted by adding 4 rnL of sterile water for injection to the vial labeled as containing 20 mg of daunorubicin. The vial should be gently agitated until the contents are completely dissolved. The resultant solution contains 5 rng of daunorubicin per mL. The desired dose of the reconstituted solution be withdrawn into a syringe containing 10-15 mL of 0.9% sodium chloride injection and then injected over 2-3 minutes into the tubing or sidearm of a freely flowing IV infusion of 0.9% sodium chloride or 5% dextrose injection. Small veins, swollen or edematous extremities, and areas overlying joints and tendons should be avoided as injection sites. The IV injection site and surrounding area should be observed for infiltration and vein irritation during administration of the drug. Patients should be instructed to immediately report any stinging or burning; if either occurs, the infusion should be stopped and restarted at another site, preferably in a different extremity. Following injection of daunorubicin, some clinicians recommend flushing the vein with the running IV infusion for 2-5 minutes and/or injecting 5-10 mL of IV solution into the sidearm to flush any remaining drug from the tubing. Daunorubicin hydrochloride has also been diluted in 100 mL of 0.9% sodium chloride or 5% dextrose injection and infused over 30-45 minutes. Parenteral daunorubicin hydrochloride solutions should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Dosage:
Dosage of daunorubicin hydrochloride is expressed in terms of daunorubicin. Dosage of daunorubicin must be based on the clinical and hematologic response and tolerance of the patient and whether or not other chemotherapy or radiation therapy has been or is also being used in order to obtain optimum therapeutic results with minimum adverse effects. Clinicians should consult published protocols for the dosage of daunorubicin and other chemotherapeutic agents and the method and sequence of administration.

Initially: 0.5-3 mg/kg. May be repeated at intervals of 1 or more days at 0.5-1 mg/kg.
- Doses of 2mg/kg should be spaced four or more days apart; doses of 2.5 or 3mg/kg, if used should only be given at 7 to 14 day intervals.
- Due to cardiotoxicity, the total dose administered should not exceed 20mg/kg, and the drug is therefore not suitable for maintenance therapy.
- In acute myeloblastic leukaemia, each dose should be about 2mg/kg, more or less according to effect, repeated at 4 to 7 day intervals. Doses of over 2mg/kg should be employed with extra caution and at intervals of one week or longer.
- In acute lymphoblastic leukaemia, doses of 1mg/kg may be repeated according to tolerance and effect at 1 to 4 day intervals.

MODE OF ADMINISTRATION
Injection

CONTRAINDICATION
1) In patients who have marked myelosuppression induced by previous treatment with other antitumor agents or by radiotherapy
2) In patients with impaired cardiac function
3) In patients who have previously received the full cumulative dose of daunorubicin and doxorubicin
4) In patients who are pregnant
5) Patients with previous hypersensitivity to daunorubicin

PRECAUTIONS :
Therapy with DAUNOCIN requires close patient observation and frequent complete blood count determinations. Cardiac, renal, and hepatic function should be evaluated prior to each course of treatment.
DAUNOCIN 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. Appropriate measures must be taken to control any systemic infection before beginning therapy with DAUNOCIN.
DAUNOCIN may transiently impart a red coloration to the urine after administration, and patients should be advised to expect this.
Carcinogenesis, Mutagenesis, Impairment of Fertility :
DAUNOCIN, when injected subcutaneously into mice, causes fibrosarcomas to develop at the injection site. When administered to mice orally or intraperitoneally, no carcinogenic effect was noted after 22 months of observation.
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.

WARNINGS:
Do not administer by IM/SC route
Bone Marrow: DAUNOCIN is a potent bone marrow suppressant. Suppression will occur in all patients given a therapeutic dose of this drug. Therapy with DAUNOCIN 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 DAUNOCIN, particularly in infants and children. Pre-existing heart disease and previous therapy with doxorubicin are co-factors of increased risk of DAUNOCIN-induced cardiac toxicity and the benefit-to-risk ratio of DAUNOCIN therapy in such patients should be weighed before starting DAUNOCIN. 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, then 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 DAUNOCIN 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 DAUNOCIN. However, certain changes in the electrocardiogram and a decrease in the systolic ejection fraction from pretreatment 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 limit lead QRS voltage has been associated with a significant risk of drug induced cardiornyopathy. Therefore, an electrocardiogram and/or determination of systolic ejection fraction should be performed before each course of DAUNOCIN. 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 with digitalis, diuretics, sodium restriction, and bed rest.
Evaluation of Hepatic and Renal Function: Significant hepatic or renal impairment can enhance the toxicity of the recommended doses of DAUNOCIN; therefore, prior to administration, evaluation of hepatic function and renal function using conventional clinical laboratory tests is recommended.
Extravasation at Injection Site: Extravasation of DAUNOCIN at the site of intravenous administration can cause severe local tissue necrosis

INTERACTIONS WITH OTHER MEDICAMENTS
Antigout agents (daunorubicin may raise the concentration of blood uric acid; dosage adjustment of antigout agents may be necessary to control hyperuricemia and gout; allopurinol may be preferred to prevent or reverse daunorubicin-induced hyperuricemia because of risk of uric acid nephropathy with uricosuric antigout agents)

Other bone marrow depressants or Radiation therapy (additive bone marrow depression may occur; dosage reduction may be required when two or more bone marrow depressants, including radiation, are used concurrently or consecutively)

Cyclophosphamide (concurrent use may result in increased cardiotoxicity; it is recommended that the total dose of daunorubicin not exceed 400 mg per square meter of body surface)

Doxorubicin (use of daunorubicin in a patient who has previously received doxorubicin increases the risk of cardiotoxicity; dosage adjustment is necessary. Daunorubicin should not be used in patients who have previously received complete cumulative doses of doxorubicin or daunorubicin; in patients who have previously received less than a complete cumulative dose of doxorubicin, the total cumulative dose of doxorubicin plus daunorubicin should not exceed 550 mg per square meter of body surface)

Hepatotoxic drugs (concurrent use may increase the risk of toxicity; for example, high-dose methotrexate may impair liver function and increase toxicity of subsequently administered daunorubicin)

Vaccines, live virus (because normal defense mechanisms may be suppressed by daunorubicin therapy, concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus, may increase the side/adverse effects of the vaccine virus, and/or may decrease the patient's antibody response to the vaccine; immunization of these patients should be undertaken only with extreme caution after careful review of the patient's hematologic status and only with the knowledge and consent of the physician managing the daunorubicin therapy. The interval between discontinuation of medications that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppression-causing medication used, the underlying disease, and other factors; estimates vary from 3 months to 1 year. Patients with leukemia in remission should not receive live virus vaccine until at least 3 months after their last chemotherapy. In addition, immunization with oral poliovirus vaccine should be postponed in persons in close contact with the patient, especially family members)

PREGNANCY AND LACTATION
Pregnancy Category D
Pregnancy: DAUNOCIN may cause fetal harm when administered to a pregnant woman because of its teratogenic potential. An increased incidence of fetal abnormalities parieto-occipital cranioschisis, umbilical hernias, or rachischisis) and abortions was reported in rabbits. 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 the drug, the patient should be apprised of the potential to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

SIDE EFFECTS
Dose - limiting toxicity includes myelosuppression and cardiotoxicity. Other reactions include:
Cutaneous: Reversible alopecia occurs in most patients.
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 has occasionally been reported.
Local: If extravasation occurs during administration, tissue necrosis can result at the site.
Acute Reactions: Rarely, anaphylactoid reaction, fever, chills, and skin rash can occur.

SYMPTOMS AND TREATMENT OF OVERDOSE
Although no cases of overdosage have been reported to our knowledge, overdosage may result In drastic myelosuppression and severe cardiotoxicity with or without transient reversible ECG changes leading to congestive heart failure. Treatment should be supportive and symptomatic.

STORAGE CONDITION
Store below 30°C. Protect from light

PACK SIZE
Daunocin for Inj X1 vial and 4ml Diluent

Manufacturer
KOREA UNITED PHARM. INC.
107, Gongdan-ro, Yeonseo-myeon, Sejong-si, Korea

Product registration holder
FIRST PHARMACEUTICAL SDN. BHD
20, Jalan SS 19/5, 47500 Subang Jaya, Selangor

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