PRODUCT MONOGRAPH

PrDaunorubicin Hydrochloride Injection

20 mg / 4 mL
(5 mg / mL) Daunorubicin base (as Daunorubicin Hydrochloride)
Solution for Injection
Intravenous infusion only

Antimitotic—Antibiotic

Hikma Canada Limited
5995 Avebury Road,
Suite 804, Mississauga,
Ontario L5R 3P9

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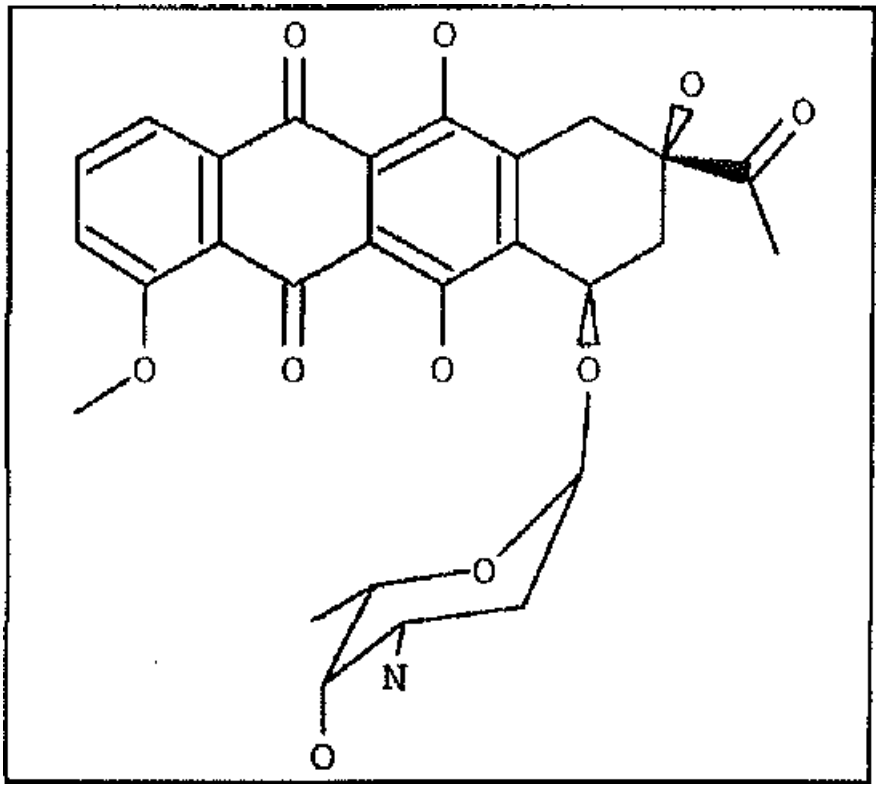
Submission Control # 259012

PHYSICAL AND CHEMICAL DESCRIPTION

Daunorubicin (R.P. 13 057) is an antibiotic produced by Streptomyces coeruleorubidis. It is the hydrochloride of 4-methoxy 6, 9, 11-trihydroxy 7, 8, 9, 10-tetrahydro (2, 3, 6-tridesoxy 3-amino L-lyxo-1-hexopyranosyl) 7-oxy-9-acetyl 5, 12-naphthacenequinone. Its structural formula is as follows:



Molecular weight: 564

The hydrochloride is an orange-red microcrystalline powder. It is soluble in water, methanol and aqueous alcohol solutions. It is practically insoluble in chloroform, ether and benzene.

PROPERTIES

Daunorubicin inhibits the synthesis of nucleic acids, both by binding desoxyribonucleic acid andby inhibiting the reproduction of desoxyribonucleic acid and the synthesis of ribonucleic acid inthe cell nucleus. As a result there is an interruption of cell division.

INDICATIONS

Daunorubicin Hydrochloride Injection is indicated in the initial treatment of myeloblastic and acute lymphoblasticleukemias. It can also induce a remission in patients suffering from chronic myeloid leukemia, reticulosarcoma, Ewing or Wilms' tumors and lymphosarcoma.

CONTRAINDICATIONS

Daunorubicin Hydrochloride Injection must not be administered to patients who exhibit myocardial lesions or to those above 75 years of age (See WARNINGS and PRECAUTIONS).

WARNINGS & PRECAUTIONS

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 Hydrochloride Injection induces medullary aplasia and leukopenia. It is therefore imperative that patients be protected against infection during the period of aplasia.

Daunorubicin treatment may lead to hyperuricaemia as a consequence of tumour lysis syndrome at the start of therapy. The increase in uric acid in the blood due to leukocyte degradation can becontrolled by administering allopurinol and liquids to stimulate urine excretion. Caution must be exercised in patients with renal insufficiency.

Cases of colitis, enterocolitis and neutropenic enterocolitis (typhlitis) have been observed in patients treated with daunorubicin. Treatment discontinuation and prompt appropriate medical management are recommended.

Daunorubicin Hydrochloride Injection can cause tissue necrosis, thus great care must be taken to inject the product directly into the vein.

When Daunorubicin Hydrochloride Injection is employed in association with other anticancer agents, the dosage of each should be reduced so as to minimize the total toxic effect.

Some instances of cardiotoxicity leading to congestive heart failure may be observed when a cumulative dose of 25 mg/kg has been reached; in general, this dose must not be exceeded except in certain desperate cases where 30 mg/kg can be administered. Likewise, because of possible cardiotoxicity, the drug must not be administered to patients who exhibit myocardial lesions or to those above 75 years of age.

Before initiating treatment with Daunorubicin Hydrochloride Injection, physical examination, appropriate x-rays and ECG should be performed and repeated at regular intervals thereafter, particularly when the cumulative dose has reached 15 mg/kg.

It is also recommended that Daunorubicin Hydrochloride Injection be employed only as a treatment to induce a remission, and not as maintenance therapy.

ADVERSE REACTIONS

At the start of treatment, the patient may experience anorexia, nausea and vomiting. These are transient effects and generally do not require an interruption of treatment. Antiemetics may help relieve vomiting.

Abdominal pain, constipation or diarrhea, alopecia, rash, petechiae or purpura may be observed during therapy.

Some cases of thrombocytopenia and anemia have been reported during the first or second weekof treatment. These phenomena are transient and corrective measures such as blood or platelet transfusions are rarely required.

During the aplastic phase, cases of localized infection have occurred, particularly in the buccal cavity and pharynx. Septicemia not responsive to antibiotics has also been reported.

Some cases of cardiopathy attended by congestive heart failure, rhythm abnormalities, electrical modifications and indications of cardiac insufficiency have been observed in patients receiving a cumulative dose exceeding 30 mg/kg.

In young patients, the urine occasionally acquires a red tint. This coloration is due to the presence of Daunorubicin Hydrochloride Injection and its metabolites and has no clinical significance.

During treatment with combinations of Daunorubicin Hydrochloride Injection with other antileukemic agents, there have been occurrences of myalgia and neuropathy. These symptoms, already associated with the use of other agents, have not been directly attributed to Daunorubicin Hydrochloride Injection.

Secondary leukaemias have been reported in patients treated with daunorubicin combination withother antineoplastics.

In every patient bone marrow function will be depressed by treatment with daunorubicin and in avariable proportion of cases, severe aplasia will develop. The consequence may include severe infection and opportunistic infection.

Serious infection is a very common risk (including sepsis, septic shock and pneumonia), which sometimes can be fatal.

Tumour lysis syndrome has been observed during daunorubicin treatment.

Cases of colitis, neutropenic enterocolitis (typhlitis), enterocolitis have been reported.

PHARMACOLOGY

Daunorubicin inhibits the synthesis of nucleic acids; its effect on desoxyribonucleic acid is particularly rapid and marked. Ribonucleic acid is more gradually affected.

It appears that the action of the drug is the result of the formation of a complex with desoxyribonucleic acid in the cell nucleus; this blocks the site of action of the polymerases and gives daunorubicin a cytostatic activity. Daunorubicin displays an immunosuppressive action as demonstrated by the inhibition of the production of heterohemagglutinins, by the prolongation of tolerance of skin grafts in mice and by the marked reduction of systemic lesions and arthritis provoked by Freund's complete adjuvant in the rat. Nevertheless, at non-toxic doses (1.25 mg/kgI.P.) daunorubicin does not decrease the number of immunologically active splenic cells in the mouse.

Daunorubicin has no effect on respiration or cellular glycolysis up to elevated concentrations which would inhibit cell growth.

In vitro, up to a concentration of 2.3 mcg/mL, daunorubicin partially inhibits KB cells cultivated instationary tubes and exerts a total inhibition at a concentration of 4.6 mcg/mL.

It exerts an antiviral effect on the herpes and on the vaccine viruses of the desoxyribonucleic acidgroup, but not on the polio or influenza virus of the ribonucleic acid group.

In vivo, in the mouse, chicken and rabbit, daunorubicin provides a variable anti-tumor activity on grafted tumors and on tumors which appear either spontaneously or as a result of a virus.

In the mouse, it exerts a potent effect (I.V., I.P.) on grafted mammary adenomas, a moderate effect on pulmonary papillary adenomas, but only a slight effect on solid Ehrlich adenocarcinoma at a dose of 3mg/kg S.C. for 6 days. By the I.P. route, daunorubicin is effective against tumors and by the S.C. route, against solid sarcomas when treatment is instituted immediately after the graft.

The drug possesses a significant inhibitory action on the Shope fibroma when administered bythe S.C. route in the rabbit.

In the reticulosarcoma of mice, daunorubicin, administered by the I.P. route, reduces the weight of the spleen by 55% and prolongs the life of the animal by 25%. Administered I.P., daunorubicinis also extremely effective in lymphoblastic leukemia and demonstrates a good effect on C 1498 myeloid leukemia. It is also very active by the I.P. route in L 1210 leukemia and Rauscher leukemia.

In the anesthetized dog, a dose of 5 mg/kg I.V. of daunorubicin does not produce any significant changes in arterial pressure and no effects were observed on the ECG or pulse. However, the same dose in the dog under pentobarbital anesthesia with atropine, produces an immediate and sustained (4 to 20 hours)
reduction (10%) of cardiac rhythm, but without appreciably affecting the contracting force of the right ventricle, the blood pressure, or respiratory rate and amplitude. The drug exerts no clear effect on the sympathetic and parasympathetic systems.

Daunorubicin is inactive when administered orally.

TERATOGENICITY STUDIES

No teratological effects have been observed in the chicken embryo, even at embryotoxic doses.In the mouse, prolonged treatment at a dose of 1.15 mg/kg S.C. daily did not interfere with gestation or produce any teratogenic effects.

In rabbits, doses of 0.09 mg/kg and 0.25 mg/kg I.V. induced 66% and 100% abortions respectively; in some fetuses, abnormalities which could not be attributed to drug, were observed.

Acute toxicity – The acute toxicity of daunorubicin is approximately 20 mg/kg in the mouse, 6mg/kg in the guinea pig, 4 mg/kg in the dog and between 12.5 and 25 mg/kg in the rat. The animals usually died from the third post-drug day. No particular toxic symptoms were observed, except that the animals languished in a state of profound torpor.

Chronic toxicity – Daily injections of 0.25, 0.50 and 1 mg/kg I.V. for 3 months in the rabbit didnot produce mortality. The appearance and behavior of the animals remained normal. At the 1mg/kg dose, anemia, benign leukopenia and a slight slowing in weight gain were observed, but these effects disappeared spontaneously by the sixth week. At higher doses (2 mg/kg), the animals dies between the 4^{th} and the 10^{th} day.

In the dog, a daily dose of 0.25 mg/kg for 3 months was well tolerated. No abnormalities were observed in the hemogram or bone marrow but there were testicular alterations with apparently irreversible total aspermatogenesis. At more elevated dosages (0.5 and 1 mg/kg), tolerance is rather poor with marked harmful effects on the blood.

DOSAGE AND ADMINISTRATION

Daunorubicin Hydrochloride Injection is reserved mainly for the initial therapy of acute leukemia and other forms of malignant tumors which are sensitive to the drug.

It is administered by the I.V. route only. Daunorubicin Hydrochloride Injection is injected into the tubing of a running infusion of 100 or 250 mL isotonic solution. The infusion is performed rapidly to avoid local stasis.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion."

Initial treatment

A) Daunorubicin Hydrochloride Injection alone

Acute lymphoblastic leukemia - Daunorubicin Hydrochloride Injection is instituted at a daily dose of 1 mg/kg (30 mg/m^2) over a period of 3 to 6 days. If, after this first administration, the number of white cells is less than 1 500, maintenance therapy is begun. However, if a partial remission is obtained, but the number of leukocytes is greater than 1 500, treatment should be repeated 1 or more times, as necessary, based on the hematological response. As soon as the remission is obtained, maintenance treatment can be started. The total dose during the

initial treatment should not, asa rule, exceed 20 mg/kg.

Acute myeloblastic, granulocytic and promyelocytic leukemias - A daily dose of 2 mg/kg (60 mg/m ^{2}) is administered for a period of 3 to 6 days, plus 1 or 2 supplementary injections which are given a few days after a remission is obtained if the blasts have not completely disappeared from the peripheral blood or marrow. The total dose varies from 3 to 22.5 mg/kg(90 to 600 mg/m ^{2}). During the initial therapy, blood should be examined every day and marrow2 or 3 times a week.

B) Combination therapy

When Daunorubicin Hydrochloride Injection is given in association with other antileukemic medication, it must be given every 2 or 3 days to avoid complete marrow aplasia; the treatment extends for a period of 2 to4 weeks. It is recommended that hemograms be conducted before each injection and if they manifest a severe perturbation of the blood count, the medication should be stopped.

The dosage is from 1 mg/kg per injection every 2 or 3 days up to a total of 12 mg/kg. If only an incomplete remission is obtained after this treatment, Daunorubicin Hydrochloride Injection can be continued up to the maximum dose of 20 mg/kg which must not be exceeded during any one treatment period. As soon as a complete remission is obtained the drug is withdrawn and maintenance treatment instituted.

Maintenance therapy

Any standard chemotherapeutic agent may be employed during maintenance therapy. If the marrow is not completely ablastic in the course of 4 weeks, a weekly injection of 1 mg/kg daunorubicin may be given.

Cumulative Doses

As a rule the total cumulative dose should not exceed 25 mg/kg, e.g., approximately 500 mg/m ^{2} for a child of 10 kg; 600 mg/m ^{2} for a child of 20 kg; 750 mg/m ^{2} for a child of 30 kg and 900 mg/m ^{2} for an adult of 60 kg. In patients who have become resistant to all therapy and for whom a final effort is required to induce a remission, the total cumulative dose can be extended to 30 mg/kg.

Chronic Myeloid Leukemia

Injections of 1 to 2 mg/kg may be administered every day or every other day up to a total doseof 6 to 12 mg/kg.

VIAL COMPOSITION

Each **4 m**L vial contains:

- medicinal ingredient: 20 mg daunorubicin base (as daunorubicin hydrochloride)
- non-medicinal ingredients: sodium chloride, sodium hydroxide, hydrochloric acid, water for injection.

Each mL of solution contains 5 mg of daunorubicin base.

AVAILABILITY OF DOSAGE FORM AND PACKAGING

Daunorubicin Hydrochloride Injection, 5 mg / mL, is available as a deep red, sterile, preservative-free solution supplied in glass vials with rubber stoppers as follows: 20 mg, 4 mL per vial, single-use vials in cartons of 1 vial.

Absence of dry natural rubber ingredients in the stoppers

STABILITY AND STORAGE RECOMMENDATIONS

Store unopened vials between 2° to 8°C. Protect from light.

SPECIAL HANDLING INSTRUCTIONS

Daunorubicin Hydrochloride Injection is a cytotoxic drug. Daunorubicin Hydrochloride Injection should be prepared for administration by professionals in a designated area for the reconstitution of cytotoxic agents. Appropriate protective clothing, including surgical gloves and goggles, should be worn. In case of contact with skin or mucosa, wash immediately with soap and water. For splashes in the eyes irrigate with clean water, holding the eyelids apart, for at least 10 minutes and seek medical attention. Any spillage should be cleared up using standard procedures consistent with the handling of chemotherapeutic agents. Waste material and any unused injection should be disposed of by incineration in a manner consistent with the handling of cytotoxic agents.

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