PRODUCT MONOGRAPH

[Pr]DAUNORUBICIN HYDROCHLORIDE FOR INJECTION

20 mg daunorubicin per vial

USP

Antimitotic – Antibiotic

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9
Canada

Date of Preparation:
November 19, 2013

Control No.: 168893

PRODUCT MONOGRAPH

[Pr]DAUNORUBICIN HYDROCHLORIDE FOR INJECTION

20 mg daunorubicin per vial

USP

THERAPEUTIC CLASSIFICATION

Antimitotic-Antibiotic

DAUNORUBICIN HYDROCHLORIDE FOR INJECTION MUST BE USED BY QUALIFIED PRACTITIONERS ONLY, OR UNDER THEIR DIRECT SUPERVISION.

ACTION AND CLINICAL PHARMACOLOGY

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.

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

INDICATIONS AND CLINICAL USE

DAUNORUBICIN is indicated in the initial treatment of myeloblastic and acute lymphoblastic leukemias. It can also induce a remission in patients suffering from chronic myeloid leukemia, reticulosarcoma, Ewing or Wilms tumors and lymphosarcoma.

PRECAUTIONS

There is limited but increasing evidence and concern that personnel involved in preparation and administration of parenteral antineoplastics may be at some risk because of the potential mutagenicity, teratogenicity, and/or carcinogenicity of these agents, although the actual risk is unknown. Cautious handling both in preparation and disposal of antineoplastic agents is recommended. Precautions that have been suggested include:

- Use of a biological containment cabinet during reconstitution and dilution of parenteral medications and wearing of disposable surgical gloves and masks.
- Use of proper technique to prevent contamination of the medication, work area, and operator during transfer between containers (including proper training of personnel in this technique).
- Cautious and proper disposal of needles, syringes, vials, ampules, and unused medication.

If extravasation of daunorubicin occurs during intravenous administration, as indicated by local burning or stinging, the injection and infusion should be stopped immediately and resumed, completing the dose in another vein.

It is recommended that the dosage of daunorubicin 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	Recommended Dose II
1.2 to 3.0 mg%	>3 mg%	75% normal dose
>3 mg%	>3 mg%	50% normal dose

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

At the start of therapy, the increase in uric acid in the blood due to leukocyte degradation can be controlled by administering allopurinol and liquids to stimulate urine excretion. Caution must be exercised in patients with renal insufficiency.

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

When daunorubicin is employed in association with other anti-cancer agents, the dosage of each should be reduced so as to minimize the total toxic effect.

Some instances of cardio-toxicity may be observed when a cumulative dose of 25 mg/kg (750 mg/m2) has been reached; in general, this dose must not be exceeded except in certain desperate cases where 30 mg/kg (900 mg/m2) can be administered. Likewise, because of possible cardio-toxicity, 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, 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 (450 mg/m2).

Mugga scans should be performed prior to, during and following therapy.

It is also recommended that daunorubicin 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 week of treatment. These phenomena are transient and corrective measures such as blood or platelet transfusions are rarely required.

Leukopenia occurs in all patients. The nadir of the leukocyte count occurs 10 to 14 days after a dose. Recovery usually occurs within 21 days after a dose.

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 rhythm abnormalities, electrical modifications and indications of cardiac insufficiency have been observed in patients receiving a cumulative dose exceeding 30 mg/kg (900 mg/m2).

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

During treatment with combinations of daunorubicin 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.

DOSAGE AND ADMINISTRATION

DAUNORUBICIN 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 intravenous route only. After dilution in 4 mL of sterile water for injection, daunorubicin is injected into the tubing of a running infusion of 100 or 250 mL isotonic solution. The infusion is performed rapidly (approximately 30 to 45 minutes) to avoid local stasis.

Freshly prepared solution may be kept for a period of 24 hours at room temperature or 48 hours in a refrigerator.

The dosage of daunorubicin must be individualized to the patient's response and tolerance and also other combined chemotherapy. In adults, the usual dose ranges from 30 to 60 mg/m^2/day for three to five days. As a single agent, a dose of 60 mg/m^2/day for three successive days repeated every three to four weeks has been recommended.

In children older than two years, the usual dose administered in combination therapy ranges from 25 to 45 mg/m^2 at varying intervals. In children younger than two years or with a body surface area less than 0.5 m^2, a dosage of 1 mg/kg should be used.

Initial Treatment

A) Daunorubicin Alone

Acute Lymphoblastic Leukemia

Daunorubicin 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 1500, maintenance therapy is begun. However, if a partial remission is obtained, but the number of leukocytes is greater than 1500, treatment should be repeated one 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, as a rule, exceed 20 mg/kg (600 mg/m^2).

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 one or two 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 - 600 mg/m^2). During the initial therapy, blood should be examined every day and marrow 2 or 3 times a week.

B) Combination Therapy

When daunorubicin 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 to 4 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 (30 mg/m^2) per injection every 2 or 3 days up to a total of 12 mg/kg (360 mg/m^2). If only an incomplete remission is obtained after this treatment, daunorubicin can be continued up to the maximum dose of 20 mg/kg (600 mg/m^2) which must not be exceeded during anyone treatment period. As soon as a complete remission is obtained, the drug is withdrawn and maintenance treatment instituted.

Maintenance Therapy

Any standard chemotherapeutic agents 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 dose of 6 to 12 mg/kg.

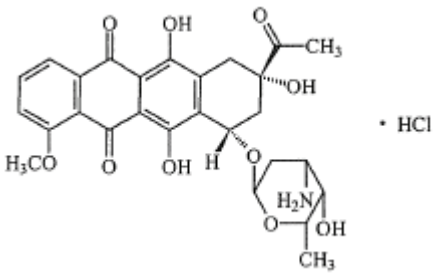
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Daunorubicin hydrochloride

Chemical Name: 5, 12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,1 O-tetrahydro-6,8,11-trihydroxy-1methoxy-,(8S-cis)-, hydrochloride
or:
(1S,-3S)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacenyl 3-amino-2,3,6-trideoxy- α-L-lyxo-hexopyranoside hydrochloride

Chemical Structure:



Molecular Formula: $C_{27}H_{29}NO_{10} \bullet HCl$

Molecular Weight: 564.0

Description: Daunorubicin hydrochloride USP is an orange-red crystalline hygroscopic powder. Upon microscopic examination, the material appears as thin red needles. The drug is soluble in water, slightly soluble in alcohol, and has a pKa of 10.3. The drug substance has a melting range of 225°C to 230°C (with decomposition). When reconstituted to 5 mg/mL, the solutions have a pH of 4.5 to 6.5.

Composition: Each vial of Daunorubicin Hydrochloride for Injection, USP contains 20 mg of daunorubicin as daunorubicin hydrochloride as well as the following non-medicinal ingredient: Mannitol, USP 100 mg.

Reconstitution:

Daunorubicin Hydrochloride for Injection, USP is reconstituted by adding 4 mL of Sterile Water for Injection to the vial labelled as containing 20 mg of daunorubicin, as daunorubicin hydrochloride. The resultant solution contains 5 mg of daunorubicin per

mL. The vial should be gently agitated until the contents are completely dissolved. Vials are for single use only, discard any unused portion.

Stability and Storage Recommendations:

The unreconstituted vial should be stored at controlled room temperature (15°-30°C), protected from light. Daunorubicin hydrochloride solutions are stable for 24 hours at room temperature (25°-30°C) or 48 hours when refrigerated at 2-8°C. After reconstitution, the solution should be protected from sunlight. Daunorubicin is unstable in solutions with pH> 8; decomposition is indicated by a colour change from red to blue-purple.

AVAILABILITY OF DOSAGE FORMS

[Pr]Daunorubicin Hydrochloride for Injection, USP is supplied as a sterile lyophilized powder with mannitol in vials containing 20 mg of daunorubicin as daunorubicin hydrochloride.

PHARMACOLOGY

DAUNORUBICIN inhibits the synthesis of nucleic acids; its effect on deoxyribonucleic 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 deoxyribonucleic acid in the cell nucleus; this blocks the site of action of the polymerases and gives daunorubicin a cytostatic activity.

Daunorubicin displays an immuno-suppressive 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/kg I.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 µg/mL, daunorubicin partially inhibits KB cells cultivated in stationary tubes and exerts a total inhibition at a concentration of 4.6 µg/ml.

It exerts an antiviral effect on the herpes and vaccine viruses of the deoxyribonucleic acid group, 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 3 mg/kg S.C. for 6 days. By the I.P. route, daunorubicin is effective against ascitic 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 by the 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., daunorubicin is 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.

TOXICOLOGY

Acute Toxicity

The acute toxicity of daunorubicin is approximately 20 mg/kg in the mouse, 6 mg/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 did not produce mortality. The appearance and behaviour of the animals remained normal. At the 1 mg/kg dose, anemia, benign leukopenia and a slight slowing in weight gain were observed, but these effects disappeared spontaneously by sixth week. At higher doses (2 mg/kg), the animals died between the 4th and 10th 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.

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 the drug, were observed.

REFERENCES

Bernard, J. and Jacquillat, C. La rubidomycine. Nouvelle Revue Française d'Hématologie, 7, (3), 317-320, 1967.

Boiron, M., Jacquillat, C., Weil, M., Thomas, M. and Bernard, J. Traitment des leucémies aiguës granulocytaires par la rubidomycine. Path-Biol., 15, (19-20), 921-924, 1967.

Bornstein, R.S., Theologides, A. and Kennedy, B.J. Daunorubicin in acute myelogenous leukemia in adults. JAMA, 207, (7), February 17, 1969.

Di Marco, A. and Massino, L. La daunomicina. Minerva Medica, .59, (69), August 29, 1968.

Dreyfus, B., Sultan, C., Boiron, M., Jacquillat, C., Weil, M. and Rochang, H. Sur le traitement d'attaque par la rubidomycine de 19 cas de leucémie aiguë myeloblastique. Presse Méd., 76, (2), 55-57, January 13, 1968.

Hardisty, R.M. and Norman, P.M. Preliminary experience with rubidomycin in the treatment of acute lymphoblastic leukemia resistant to other antimetabolites. Path-Biol., 15, (19-20), 941942, 1967.

Holland, J.F. Daunomycin treatment in acute leukemia. Path-Biol., 15, (19-20), 929-932, 1967.

Julou, L., Ducrot, R., Fournel, J., Ganter, P., Maral, R., Populaire, P., Koenig, F., Myon, J., Pascal, S. and Pasquet, J. Un nouvel antibiotique doué d'activité antitumorale: la rubidomycine (13 057 R.P.) - III - Etude toxocologique it pharmacologique. Arzneimittel Forschung, 17, 948-954, 1967.

Kourilsky, F.M., Dupuy, J.M., Fradelizi, D., Jacquillat, CL and Bernard, J. Abolition des reactions d'hypersensibilité retardée et gravité des aplasies induites par la rubidomycine. Path-Biol., 15, (19-20), 959, 1967.

Kreiter, H., Begemann, H. and Rastetter, J. Bilan du traitement de leucemies aiguës myeloblastiques par la daunomycine et la cytosine arabinoside. Medizinische Klinik, .5-1, 2058-2066, 1968.

Macrez, CI., Marneffe-Lebrequier, H., Ripault, J., Clauvel, J.P., Jacquillat, CI., and Weil, M. Accidents cardiaques observées au cours des traitements par la rubidomycine. Path-Biol., 15, (19-20), 949-953, 1967.

Mathe, G., Schwarzenberg, L., Schneider, M., Schlumberger, J.R., Hayat, M., Amiel, J.L., Cattan, A. and Jasmin, C. Acute lymphoblastic leukemea treated with a combination of prednisone, vincristine and rubidomycin. The Lancet, 380-382, August 19, 1967.

Tan, C., Tasaka, H., Yu, K.P., Murphy, L., and Karnofsky, D. Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease. Cancer, 20, 333-353, March 1967.