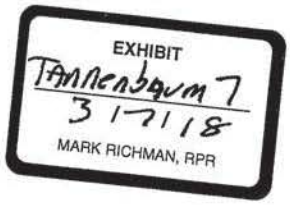
PHYSICIANS' DESK REFERENCE®



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Astra—Cont.

Dalgan, like other mixed agonist-antagonist opioid analgesics, has low abuse potential in patient populations. However, strong mixed agonist-antagonist drugs have reportedly been associated with abuse and dependence in health-care providers and others with ready access to such drugs. Dalgan should be handled accordingly.

Manufactured by:
Wyeth Laboratories Inc.
Philadelphia, PA 19101
Manufactured for:
Astra USA, Inc.
Westboro, MA 01581
021575R00 (8/94)

50% DEXTROSE ℞

[dex 'trose]
Injection, USP
Concentrated Dextrose
For Intravenous Administration

NOTE: This solution is hypertonic—see WARNINGS and PRECAUTIONS

(For details of indications, dosage and administration, precautions, and adverse reactions, see circular in package.)

HOW SUPPLIED

50% Dextrose Injection, USP is supplied as follows:
50 mL Prefilled Syringe with 19 G 15/16" needle, NDC 0186-0654-01
The solution should be stored at controlled room temperature 15°-30°C (59°-86°F).
021857R06 Rev. 10/94 (6)

DOBUTAMINE HYDROCHLORIDE INJECTION ℞

DESCRIPTION

Dobutamine Hydrochloride Injection is 1,2-benzenediol, 4-[2-[[3-(4-hydroxyphenyl)-1-methylpropyl] amino]ethyl]-, hydrochloride, (±)-. It is a synthetic catecholamine.

Molecular Formula: $C_{18}H_{23}NO_3 \cdot HCl$
Molecular Weight: 337.85

The clinical formulation is supplied in a sterile form for intravenous use only. Each mL contains dobutamine hydrochloride equivalent to 12.5 mg (41.5 μmol) dobutamine, 0.24 mg sodium metabisulfite (added during manufacture), and water for injection, q.s. Hydrochloric acid and/or sodium hydroxide may have been added during manufacture to adjust the pH.
Single dose vial. Discard unused portion.

HOW SUPPLIED

NDC 0186-1931-01, 20 mL single dose vial containing 250 mg dobutamine (as the hydrochloride), box of 1.
Store at controlled room temperature 15°-30°C (59°-86°F).
Caution: Federal law prohibits dispensing without prescription.
021648R03 Iss. 8/94

DOPAMINE HCl Injection, USP ℞

[dó-pa-mean]

(For details of indications, dosage and administration, precautions, and adverse reactions, see circular in package.)

HOW SUPPLIED

Dopamine HCl 200 mg is supplied in the following form:
Additive Syringe 5 mL (40 mg/mL) NDC 0186-0638-01
Dopamine HCl 400 mg is supplied in the following forms:
Additive Syringe 5 mL (80 mg/mL) NDC 0186-0641-01
10 mL (40 mg/mL) NDC 0186-0639-01
Dopamine HCl 800 mg is supplied in the following form:
Additive Syringe 5 mL (160 mg/mL) NDC 0186-0642-01
Packages are color coded according to the total dosage content; 200 mg coded blue/white, 400 mg coded green/white and 800 mg coded yellow/white.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
Avoid contact with alkalies (including sodium bicarbonate), oxidizing agents, or iron salts.
NOTE: Do not use the Injection if it is darker than slightly yellow or discolored in any way.
021861R07 3/92 (7)

DOXORUBICIN HYDROCHLORIDE INJECTION, USP
DOXORUBICIN HYDROCHLORIDE FOR INJECTION, USP ℞

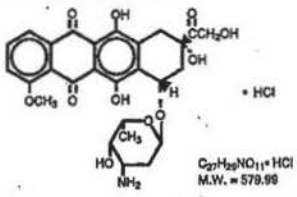
[dox-ō-rūbe'-ih-sin]
FOR INTRAVENOUS USE ONLY

WARNINGS

1. Severe local tissue necrosis will occur if there is extravasation during administration (see DOSAGE AND ADMINISTRATION). Doxorubicin must not be given by the intramuscular or subcutaneous route.
2. Serious irreversible myocardial toxicity with delayed congestive failure often unresponsive to any cardiac supportive therapy may be encountered as total dosage approaches 550 mg/m². This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy.
3. Dosage should be reduced in patients with impaired hepatic function.
4. Severe myelosuppression may occur.
5. Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *cæsius*. Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine. The structural formula is a follows:



$C_{27}H_{29}NO_{11} \cdot HCl$
M.W. = 579.99

Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic but the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino sugar, producing a hydrophilic center. The molecule is amphoteric, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. It binds to cell membranes as well as plasma proteins.
Doxorubicin Hydrochloride Injection, USP is a sterile, isotonic, preservative-free solution for intravenous administration. It is available in 10 mg (5 mL), 20 mg (10 mL), 50 mg (25 mL) single dose vials and 2 mg/mL (100 mL) multi-dose vials. Each mL contains 2 mg doxorubicin hydrochloride and the following inactive ingredients: sodium chloride 9 mg and water for injection q.s. Hydrocholoric acid is used to adjust pH to a target pH of 3.0.
Doxorubicin Hydrochloride for Injection, USP, is supplied as a sterile, lyophilized powder in vials containing 10 mg, 20 mg, or 50 mg of doxorubicin hydrochloride, which, when reconstituted according to directions with a suitable diluent, produces a sterile, isotonic solution, for intravenous administration, containing 2 mg/mL of doxorubicin hydrochloride. Each vial also contains 50 mg, 100 mg, or 250 mg, respectively, of lactose monohydrate.

CLINICAL PHARMACOLOGY

Though not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations. Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy to testes in rats and dogs.
Pharmacokinetic studies show the intravenous administration of normal or radiolabeled doxorubicin is followed by rapid plasma clearance and significant tissue binding. Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4 to 5% of the administered dose in five days. Biliary excretion represents the major excretion route, 40 to 50% of the administered dose being recovered in the bile or feces in seven days. Impairment of liver function results in slower excretion, and consequently, increased retention and accumulation in plasma and tissues. Doxorubicin does not cross the blood brain barrier.

INDICATIONS AND USAGE

Injectable doxorubicin hydrochloride has been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, lymphomas of both Hodgkin and non-Hodgkin types, bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types and gastric carcinoma.
A number of other solid tumors have also shown some responsiveness but in numbers too limited to justify specific recommendation. Studies to date have shown malignant melanoma, kidney carcinoma, large bowel carcinoma, brain tumors and metastases to the central nervous system not to be significantly responsive to doxorubicin therapy.

CONTRAINDICATIONS

Doxorubicin therapy should not be started in patients who have marked myelosuppression induced by previous treatment with other antitumor agents or by radiotherapy. Conclusive data are not available on pre-existing heart disease as a co-factor of increased risk of doxorubicin induced cardiac toxicity. Preliminary data suggest that in such cases cardiac toxicity may occur at doses lower than the recommended cumulative limit. It is therefore not recommended to start doxorubicin in such cases. Doxorubicin treatment is contraindicated in patients who received previous treatment with complete cumulative doses of doxorubicin and/or daunorubicin.

WARNINGS

Special attention must be given to the cardiac toxicity exhibited by doxorubicin. Although uncommon, acute left ventricular failure has occurred, particularly in patients who have received total dosage of the drug exceeding the currently recommended limit of 550 mg/m². This limit appears to be lower (400 mg/m²) in patients who received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. The total dose of doxorubicin administered to the individual patient should also take into account previous or concomitant therapy with related compounds such as daunorubicin. Congestive heart failure and/or cardiomyopathy may be encountered several weeks after discontinuation of doxorubicin therapy.
Cardiac failure is often not favorably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of drug induced heart failure appears to be essential for successful treatment with digitalis, diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent ECG changes. A baseline ECG and ECGs performed prior to each dose or course after 300 mg/m² cumulative dose has been given is suggested. Transient ECG changes consisting of T-wave flattening, S-T depression and arrhythmias lasting up to two weeks after a dose or course of doxorubicin are presently not considered indications for suspension of doxorubicin therapy. Doxorubicin cardiomyopathy has been reported to be associated with a persistent reduction in the voltage of the QRS wave, a prolongation of the systolic time interval and a reduction of the ejection fraction as determined by echocardiography or radionuclide angiography. None of these tests have yet been confirmed to consistently identify those individual patients that are approaching their maximally tolerated cumulative dose of doxorubicin. If test results indicate change in cardiac function associated with doxorubicin, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.
Acute life-threatening arrhythmias have been reported to occur during or within a few hours after doxorubicin hydrochloride administration.
There is a high incidence of bone marrow depression, primarily of leukocytes, requiring careful hematologic monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir at 10 to 14 days after treatment with recovery usually occurring by the 21st day. White blood cell counts as low as 1000/mm³ are to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or suspension or delay of doxorubicin therapy. Persistent severe myelosuppression may result in superinfection or hemorrhage.
Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported. Radiation induced toxicity to the myocardium, mucosae, skin and liver have been reported to be increased by the administration of doxorubicin.

Toxicity to recommended doses of doxorubicin hydrochloride is enhanced by hepatic impairment, therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional clinical laboratory tests, such as SGOT, SGPT, alkaline phosphatase and bilirubin. (See DOSAGE AND ADMINISTRATION.)

Necrotizing colitis manifested by typhlitis (cecal inflammation), bloody stools and severe and sometimes fatal infections have been associated with a combination of doxorubicin hydrochloride given by IV push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation and even if blood returns well on aspiration of the infusion needle (see DOSAGE AND ADMINISTRATION). If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein.

Doxorubicin and related compounds have also been shown to have mutagenic and carcinogenic properties when tested in experimental models.

Usage in pregnancy—Safe use of doxorubicin has not been established. Doxorubicin is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. Therefore, the benefits to the pregnant patient should be carefully weighed against the potential toxicity to fetus and embryo. The possible adverse effects on fertility in males and females in humans or experimental animals have not been adequately evaluated.

PRECAUTIONS

Initial treatment with doxorubicin requires close observation of the patient and extensive laboratory monitoring. It is recommended, therefore, that patients be hospitalized at least during the first phase of the treatment.

Like other cytotoxic drugs, doxorubicin may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

Doxorubicin imparts a red coloration to the urine for 1 to 2 days after administration and patients should be advised to expect this during active therapy.

Doxorubicin is not an anti-microbial agent.

ADVERSE REACTIONS

Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity (see WARNINGS). Other reactions reported are:

Cutaneous—Reversible and complete alopecia occurs in most cases.

Hyperpigmentation of nailbeds and dermal creases, primarily in children, and onycholysis have been reported in a few cases. Recall of skin reaction due to prior radiotherapy has occurred with doxorubicin administration.

Gastrointestinal—Acute nausea and vomiting occurs frequently and may be severe. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur 5 to 10 days after administration. The effect may be severe leading to ulceration and represents a site of origin for severe infections. The dosage regimen consisting of administration of doxorubicin on three consecutive days results in the greater incidence and severity of mucositis. Ulceration and necrosis of the colon, especially the cecum, may occur leading to bleeding or severe infections which can be fatal. This reaction has been reported in patients with acute non-lymphocytic leukemia treated with a 3-day course of doxorubicin combined with cytarabine. Anorexia and diarrhea have been occasionally reported.

Vascular—Phlebosclerosis has been reported especially when small veins are used or a single vein is used for repeated administration. Facial flushing may occur if the injection is given too rapidly.

Local—Severe cellulitis, vesication and tissue necrosis will occur if doxorubicin is extravasated during administration. Erythematous streaking along the vein proximal to the site of the injection has been reported. (See DOSAGE AND ADMINISTRATION.)

Hypersensitivity—Fever, chills and urticaria have been reported occasionally. Anaphylaxis may occur. A case of apparent cross sensitivity to lincomycin has been reported.

Other—Conjunctivitis and lacrimation occur rarely.

OVERDOSAGE

Acute overdosage of doxorubicin enhances the toxic effects of mucositis, leukopenia and thrombopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis. The 200 mg vial is packaged as a multiple dose vial and caution should be exercised to prevent inadvertent overdosage.

Chronic overdosage with cumulative doses exceeding 550 mg/m^2 increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. The use of peripheral vasodilators has been recommended.

DOSAGE AND ADMINISTRATION

Care in the administration of doxorubicin hydrochloride will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation and even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If it is known or suspected that subcutaneous extravasation has occurred, local infiltration with an injectable corticosteroid and flooding the site with normal saline has been reported to lessen the local reaction. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained. If ulceration begins, early wide excision of the involved area should be considered[1].

The most commonly used dosage schedule is 60 to 75 mg/m^2 as a single intravenous injection administered at 21 day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dosage schedule is weekly doses of 20 mg/m^2 which has been reported to produce a lower incidence of congestive heart failure. Thirty (30) mg/m^2 on each of three successive days repeated every four weeks has also been used. Doxorubicin dosage must be reduced if the bilirubin is elevated as follows: serum bilirubin 1.2 to 3.0 mg/dL—give ½ normal dose, >3 mg/dL—give ¼ normal dose.

Reconstitution Directions: Doxorubicin Hydrochloride for Injection, 10 mg, 20 mg and 50 mg vials should be reconstituted with 5 mL, 10 mL and 25 mL, respectively, of Sodium Chloride Injection 0.9% to give a final concentration of 2 mg/mL of doxorubicin hydrochloride. An appropriate volume of air should be withdrawn from the vial during reconstitution to avoid excessive pressure build-up. Bacteriostatic diluents are not recommended.

After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration 2°C to 8°C (36°F to 46°F). It should be protected from exposure to sunlight. Discard any unused solution from the 10 mg, 20 mg and 50 mg single dose vials.

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

It is recommended that doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection or Dextrose Injection, 5%. The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein and the dosage. However, the dose should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly. Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data are available, it is not recommended that doxorubicin be mixed with other drugs. Doxorubicin has been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated.

Handling and Disposal: Skin reactions associated with doxorubicin have been reported. Caution in the handling and preparation of the powder and solution must be exercised and the use of gloves is recommended. If doxorubicin powder or solution contacts the skin or mucosae, immediately wash thoroughly with soap and water.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[2-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Doxorubicin Hydrochloride Injection, USP, is supplied as a sterile, red-orange solution. Single dose vial, contains no preservatives. Discard unused portion.

NDC 0186-1532-31			
10 mg vial,	2 mg/mL,	5 mL,	Box of 1.
NDC 0186-1532-41			
20 mg vial,	2 mg/mL,	10 mL,	Box of 1.
NDC 0186-1532-61			
50 mg vial,	2 mg/mL,	25 mL,	Box of 1.

Store under refrigeration 2°C to 8°C (36°F to 46°F). Protect from light. Retain in carton until time of use.

Multidose vial, contains no preservatives.

NDC 0186-1532-81			
200 mg vial,	2 mg/mL,	100 mL,	Box of 1.

Store under refrigeration 2°C to 8°C (36°F to 46°F). Protect from light. Retain in carton until contents are used.

Doxorubicin Hydrochloride for Injection, USP, is supplied in single dose vials as a sterile red-orange lyophilized powder. The vials are packed in individual cartons.

10 mg	NDC 0186-1533-28 Product No. 1530-13	Box of 5
20 mg	NDC 0186-1535-28 Product No. 1575-12	Box of 5
50 mg	NDC 0186-1534-28 Product No. 1531-01	Box of 1

Store unreconstituted vials at controlled room temperature 15°C to 30°C (59°F to 86°F). After reconstitution the solution is stable for 7 days at room temperature and 15 days under refrigeration 2°C to 8°C (36°F to 46°F).

Protect from light. Retain in carton until contents are used. Discard usnused portion.

Caution: Federal law prohibits dispensing without prescription.

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1. Rudolph R, et al: Skin Ulcers Due to Adriamycin. Cancer 1976;38:1087–1094.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington D.C. 20402.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA, March 15, 1985.
4. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts, 02115.
5. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia 1983: 1:426–428.
6. Jones RB, et al. Safe handling of chemotherapeutic agents: A Report from the Mount Sinai Medical Center. Ca-A Cancer Journal for Clinicians Sept./Oct., 1983: 258–263.
7. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990: 47:1033–1049.

MANUFACTURED FOR:
Astra USA, Inc.
Westborough, MA, 01581
DATE:
October 1994 021794R01
MANUFACTURED BY:
PHARMACHEMIE B.V.
Haarlem
The Netherlands 93.144.101-C

DROPERIDOL INJECTION, USP

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.

(For details of indications, dosage and administration, precautions, and adverse reactions, see circular in package.)

HOW SUPPLIED

Droperidol injection is available as:

Ampules, 2.5 mg/mL		
2 mL, (5 mg/2 mL),	box of 10	NDC 0186-1220-03
5 mL, (12.5 mg/5 mL),	box of 10	NDC 0186-1221-03
Single Dose Vials, 2.5 mg/mL		
2 mL, (5 mg/2 mL),	box of 10	NDC 0186-1226-13
5 mL, (12.5 mg/5 mL),	box of 10	NDC 0186-1227-13
Multiple Dose Vials, 2.5 mg/mL		
10 mL,	box of 1	NDC 0186-1224-12

PROTECT FROM LIGHT. STORE AT CONTROLLED ROOM TEMPERATURE 15°–30°C (59°–86°F).

021879R03 REV. 2/95

Continued on next page

Bristol-Myers Squibb Oncology—Cont.

tients receiving a relatively high cumulative dose of PLATINOL and with a relatively advanced symptomatic stage of peripheral neuropathy.

Ocular Toxicity—Optic neuritis, papilledema, and cerebral blindness have been reported infrequently in patients receiving standard recommended doses of PLATINOL. Improvement and/or total recovery usually occurs after discontinuing PLATINOL. Steroids with or without mannitol have been used; however, efficacy has not been established.

Blurred vision and altered color perception have been reported after the use of regimens with higher doses of PLATINOL or greater dose frequencies than those recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic exam is irregular retinal pigmentation of the macular area.

Anaphylactic-like Reactions—Anaphylactic-like reactions have been occasionally reported in patients previously exposed to PLATINOL. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by intravenous epinephrine with corticosteroids, and/or antihistamines as indicated. Patients receiving PLATINOL should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Hepatotoxicity—Transient elevations of liver enzymes, especially SGOT, as well as bilirubin, have been reported to be associated with PLATINOL administration at the recommended doses.

Other Events—Other toxicities reported to occur infrequently are cardiac abnormalities, hiccups, elevated serum amylase, and rash. Alopecia has also been reported.

Local soft tissue toxicity has rarely been reported following extravasation of PLATINOL. Severity of the local tissue toxicity appears to be related to the concentration of the PLATINOL solution. Infusion of solutions with a PLATINOL concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis, and necrosis.

OVERDOSAGE

Caution should be exercised to prevent inadvertent overdosage with PLATINOL. Acute overdosage with this drug may result in kidney failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, intractable nausea and vomiting and/or neuritis. In addition, death can occur following overdosage.

No proven antidotes have been established for PLATINOL overdosage. Hemodialysis, even when initiated four hours after the overdosage, appears to have little effect on removing platinum from the body because of PLATINOL's rapid and high degree of protein binding. Management of overdosage should include general supportive measures to sustain the patient through any period of toxicity that may occur.

DOSAGE AND ADMINISTRATION

Note: Needles or intravenous sets containing aluminum parts that may come in contact with PLATINOL® (cisplatin injection, USP) should not be used for preparation or administration. Aluminum reacts with PLATINOL, causing precipitate formation and a loss of potency.

Metastatic Testicular Tumors—The usual PLATINOL dose for the treatment of testicular cancer in combination with other approved chemotherapeutic agents is 20 mg/m^2 IV daily for a 5 day cycle.

Metastatic Ovarian Tumors—The usual PLATINOL dose for the treatment of metastatic ovarian tumors in combination with Cytoxan is 75–100 mg/m^2 IV per cycle once every 4 weeks (Day 1).[2,3]

The dose of Cytoxan when used in combination with PLATINOL is 600 mg/m^2 IV once every 4 weeks, (Day 1).[2,3]

For directions for the administration of Cytoxan, refer to the Cytoxan package insert.

In combination therapy, PLATINOL and Cytoxan are administered sequentially.

As a single agent, PLATINOL should be administered at a dose of 100 mg/m^2 IV per cycle once every 4 weeks.

Advanced Bladder Cancer—PLATINOL should be administered as a single agent at a dose of 50 to 70 mg/m^2 IV per cycle once every 3 to 4 weeks depending on the extent of prior exposure to radiation therapy and/or prior chemotherapy. For heavily pretreated patients an initial dose of 50 mg/m^2 per cycle repeated every 4 weeks is recommended.

Pretreatment hydration with 1 to 2 liters of fluid infused for 8 to 12 hours prior to a PLATINOL dose is recommended. The drug is then diluted in 2 liters of 5% Dextrose in ½ or ⅓ normal saline containing 37.5 g of mannitol, and infused over a 6- to 8-hour period. If diluted solution is not to be used within 6 hours, protect solution from light. Do not dilute PLATINOL in just 5% Dextrose injection. Adequate hydration and urinary output must be maintained during the following 24 hours.

A repeat course of PLATINOL should not be given until the serum creatinine is below 1.5 mg/100 mL, and/or the BUN is below 25 mg/100 mL. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets ≥ 100,000/mm^3, WBC ≥ 4,000/mm^3). Subsequent doses of PLATINOL should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.

As with other potentially toxic compounds, caution should be exercised in handling the aqueous solution. Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If cisplatin solution contacts the skin or mucosae, immediately wash the skin or mucosae thoroughly with soap and water.

The aqueous solution should be used intravenously only and should be administered by IV infusion over a 6- to 8-hour period.

NOTE TO PHARMACIST: Exercise caution to prevent inadvertent PLATINOL-AQ overdosage. Please call prescriber if dose greater than 100 mg/m^2 per cycle. Aluminum and flip-off seal of vial have been imprinted with the following statement: **CALL DR. IF DOSE > 100 MG/M^2/CYCLE.**

STABILITY

PLATINOL-AQ is a sterile, multidose vial without preservatives. Store at 15°C–25°C. Do not refrigerate. Protect unopened container from light.

The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for seven days under fluorescent room light.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[4–10] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

PLATINOL-AQ (cisplatin injection).

NDC 0015-3220-22—Each multidose vial contains 50 mg of cisplatin.

NDC 0015-3221-22—Each multidose vial contains 100 mg of cisplatin.

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3. Swenerton K, et al: Cisplatin-Cyclophosphamide versus Carboplatin-Cyclophosphamide in Advanced Ovarian Cancer: A Randomized Phase III Study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 1992; 10:718–726.
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6. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
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Shown in Product Identification Guide, page 307

(3220 DIM-14)

December 1994

RUBEX®

[*rü'-beks*]

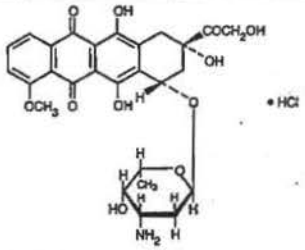
(doxorubicin hydrochloride for injection, USP)

WARNINGS

1. Severe local tissue necrosis will occur if there is extravasation during administration (see "DOSAGE AND ADMINISTRATION" section). Doxorubicin must not be given by the intramuscular or subcutaneous route.
2. Serious irreversible myocardial toxicity with delayed congestive failure often unresponsive to any cardiac supportive therapy may be encountered as total dosage approaches 550 mg/m^2. This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy.
3. Dosage should be reduced in patients with impaired hepatic function.
4. Severe myelosuppression may occur.
5. Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*. Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine. The structural formula is as follows:



$C_{27}H_{29}NO_{11} \cdot HCl$ Formula Weight—579.99

Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic but the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino sugar, producing a hydrophilic center. The molecule is amphoteric, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. It binds to cell membranes as well as plasma proteins. RUBEX® (doxorubicin hydrochloride for injection, USP) is for intravenous use only. It is available in 10 mg, 50 mg and 100 mg single dose vials as a lyophilized, sterile powder with added lactose (anhydrous), NF 50 mg, 250 mg and 500 mg respectively.

CLINICAL PHARMACOLOGY

Though not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations. Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy to testes in rats and dogs. Pharmacokinetic studies show the intravenous administration of normal or radiolabeled doxorubicin is followed by rapid plasma clearance and significant tissue binding. Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4 to 5% of the administered dose in 5 days. Biliary excretion represents the major excretion route, 40 to 50% of the administered dose being recovered in the bile or the feces in 7 days. Impairment of liver function results in slower excretion, and, consequently, increased retention and accumulation in plasma and tissues. Doxorubicin does not cross the blood brain barrier.

INDICATIONS AND USAGE

Doxorubicin hydrochloride for injection has been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, lymphomas of both Hodgkin and non-Hodgkin types, bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types and gastric carcinoma.

A number of other solid tumors have also shown some responsiveness but in numbers too limited to justify specific recommendation. Studies to date have shown malignant melanoma, kidney carcinoma, large bowel carcinoma, brain tumors and metastases to the central nervous system not to be significantly responsive to doxorubicin therapy.

CONTRAINDICATIONS

Doxorubicin therapy should not be started in patients who have marked myelosuppression induced by previous treatment with other antitumor agents or by radiotherapy. Conclusive data are not available on pre-existing heart disease as a co-factor of increased risk of doxorubicin-induced cardiac toxicity. Preliminary data suggest that in such cases cardiac toxicity may occur at doses lower than the recommended cumulative limit. It is therefore not recommended to start doxorubicin in such cases. Doxorubicin treatment is contraindicated in patients who received previous treatment with complete cumulative doses of doxorubicin and/or daunorubicin.

WARNINGS

Special attention must be given to the cardiac toxicity exhibited by doxorubicin. Although uncommon, acute left ventricular failure has occurred, particularly in patients who have received total dosage of the drug exceeding the currently recommended limit of 550 mg/m^2. This limit appears to be lower (400 mg/m^2) in patients who received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. The total dose of doxorubicin administered to the individual patient should also take into account previous or concomitant therapy with related compounds such as daunorubicin. Congestive heart failure and/or cardiomyopathy may be encountered several weeks after discontinuation of doxorubicin therapy.

Cardiac failure is often not favorably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of drug induced heart failure appears to be essential for successful treatment with digitalis, diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent EKG changes. A baseline EKG and EKGs performed prior to each dose or course after 300 mg/m^2 cumulative dose has been given is suggested. Transient EKG changes consisting of T-wave flattening, S-T depression and arrhythmias lasting for up to 2 weeks after a dose or course of doxorubicin are presently not considered indications for suspension of doxorubicin therapy. Doxorubicin cardiomyopathy has been reported to be associated with a persistant reduction in the voltage of the QRS wave, a prolongation of the systolic time interval and a reduction of the ejection fraction as determined by echocardiography or radionuclide angiography. None of these tests have yet been confirmed to consistently identify those individual patients that are approaching their maximally tolerated cumulative dose of doxorubicin. If test results indicate change in cardiac function associated with doxorubicin the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

Acute life-threatening arrhythmias have been reported to occur during or within a few hours after doxorubicin hydrochloride administration.

There is a high incidence of bone marrow depression, primarily of leukocytes, requiring careful hematologic monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir at 10 to 14 days after treatment with recovery usually occurring by the 21st day. White blood cell counts as low as 1000/mm^3 are to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or suspension or delay of doxorubicin therapy. Persistent severe myelosuppression may result in superinfection or hemorrhage.

Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported. Radiation induced toxicity to the myocardium, mucosae, skin and liver have been reported to be increased by the administration of doxorubicin.

Toxicity to recommended doses of doxorubicin hydrochloride is enhanced by hepatic impairment, therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin (see "DOSAGE AND ADMINISTRATION" section).

Necrotizing colitis manifested by typhlitis (cecal inflammation), bloody stools and severe and sometimes fatal infections have been associated with a combination of doxorubicin hydrochloride given by I.V. push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

As with intravenous administration of doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation and even if blood returns well on aspiration of the infusion needle (see "DOSAGE AND ADMINISTRATION" section). If any signs or symptoms of extravasation have occurred the injection or infusion should be immediately terminated and restarted in another vein.

Doxorubicin and related compounds have also been shown to have mutagenic and carcinogenic properties when tested in experimental models.

Usage in Pregnancy—Safe use of doxorubicin in pregnancy has not been established. Doxorubicin is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. Therefore, the benefits to the pregnant patient should be carefully weighed against the potential toxicity to fetus and embryo. The possible adverse effects on fertility in males and females in humans or experimental animals have not been adequately evaluated.

PRECAUTIONS

Initial treatment with doxorubicin requires close observation of the patient and extensive laboratory monitoring. It is recommended, therefore, that patients be hospitalized at least during the first phase of the treatment.

Like other cytotoxic drugs, doxorubicin may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

Doxorubicin imparts a red coloration to the urine for 1 to 2 days after administration and patients should be advised to expect this during active therapy.

Doxorubicin is not an antimicrobial agent.

ADVERSE REACTIONS

Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity (see "WARNINGS" section). Other reactions reported are:

Cutaneous—Reversible complete alopecia occurs in most cases. Hyperpigmentation of nailbeds and dermal creases, primarily in children, and onycholysis have been reported in a few cases. Recall of skin reaction due to prior radiotherapy has occurred with doxorubicin administration.

Gastrointestinal—Acute nausea and vomiting occurs frequently and may be severe. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur 5 to 10 days after administration. The effect may be severe leading to ulceration and represents a site of origin for severe infections. The dosage regimen consisting of administration of doxorubicin on 3 successive days results in the greater incidence and severity of mucositis. Ulceration and necrosis of the colon, especially the cecum, may occur leading to bleeding or severe infections which can be fatal. This reaction has been reported in patients with acute nonlymphocytic leukemia treated with a 3-day course of doxorubicin combined with cytarabine. Anorexia and diarrhea have been occasionally reported.

Vascular—Phlebosclrosis has been reported especially when small veins are used or a single vein is used for repeated administration. Facial flushing may occur if the injection is given too rapidly.

Local—Severe cellulitis, vesication and tissue necrosis will occur if doxorubicin is extravasated during administration. Erythematous streaking along the vein proximal to the site of the injection has been reported (see "DOSAGE AND ADMINISTRATION" section).

Hypersensitivity—Fever, chills and urticaria have been reported occasionally. Anaphylaxis may occur. A case of apparent cross sensitivity to lincomycin has been reported.

Other—Conjunctivitis and lacrimation occur rarely.

OVERDOSAGE

Acute overdosage with doxorubicin enhances the toxic effects of mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions, and symptomatic treatment of mucositis.

Chronic overdosage with cumulative doses exceeding 550 mg/m^2 increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. The use of peripheral vasodilators has been recommended.

DOSAGE AND ADMINISTRATION

Care in the administration of doxorubicin hydrochloride will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation and even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If it is known or suspected that subcutaneous extravasation has occurred, local infiltration with an injectable corticosteroid and flooding the site with normal saline has been reported to lessen the local reaction. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained. If ulceration begins, early wide excision of the involved area should be considered.[1]

The most commonly used dosage schedule is 60 to 75 mg/m^2 as a single intravenous injection administered at 21-day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dosage schedule is weekly doses of 20 mg/m^2 which has been reported to produce a lower incidence of congestive heart failure. Thirty (30) mg/m^2 on each of 3 successive days repeated every 4 weeks has also been used. Doxorubicin dosage must be reduced if the bilirubin is elevated as follows: Serum Bilirubin 1.2 to 3.0 mg/dL—give ½ normal dose, >3 mg/dL—give ¼ normal dose.

Preparation of Solution—Doxorubicin hydrochloride for injection, USP, 10 mg, 50 mg and 100 mg vials should be reconstituted with 5 mL, 25 mL and 50 mL respectively of Sodium Chloride Injection, USP (0.9%) to give a final concentration of 2 mg/mL of doxorubicin hydrochloride. An apropriate volume of air should be withdrawn from the vial during reconstitution to avoid excessive pressure build-up. Bacteriostatic diluents are not recommended.

After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration 2°–8°C (36°–46°F). It should be protected from exposure to sunlight and any unused solution should be discarded.

It is recommended that doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein and the dosage. However, the dose should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data are available, it is not recommended that doxorubicin be mixed with other drugs.

Doxorubicin has been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated.

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

Handling and Disposal—Skin reactions associated with doxorubicin have been reported. Caution in the handling and preparation of the powder and solution must be exercised and the use of gloves is recommended. If doxorubicin powder or solution contacts with skin or mucosae, immediately wash thoroughly with soap and water.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are neccesary or appropriate.

HOW SUPPLIED

RUBEX® (doxorubicin hydrochloride for injection, USP) is available as follows:

10 mg—Each single-dose vial contains 10 mg of doxorubicin HCl, USP as a sterile red-orange lyophilized powder. **NDC 0015-3351-22**

Available as individually cartoned vials in packages of 10 (10-pack).

50 mg—Each single-dose vial contains 50 mg of doxorubicin HCl, USP as a sterile red-orange lyophilized powder. **NDC 0015-3352-22**

Available as one individually cartoned vial.

100 mg—Each single-dose vial contains 100 mg of doxorubicin HCl, USP as a sterile red-orange lyophilized powder. **NDC 0015-3353-22**

Available as one individually cartoned vial.

Store dry powder at controlled room temperature 15°–30°C (59°–86°F).

The reconstituted solution is stable for 24 hours at room temperature or 48 hours under refrigeration 2°–8°C (36°–46°F). Protect from exposure to sunlight. Retain in carton until time of use.

Continued on next page

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