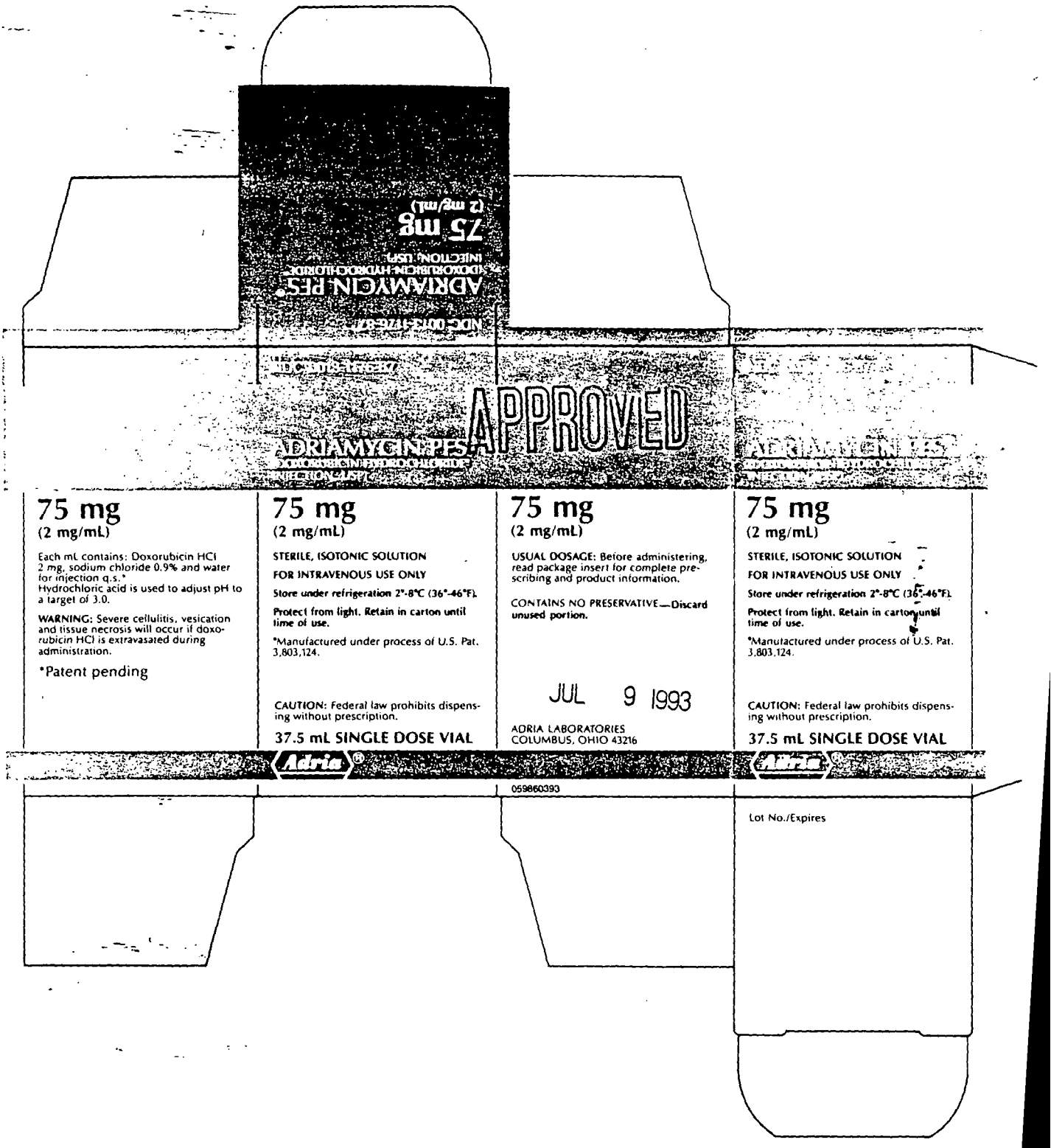
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63-165/s-3,s-5,s-6

APPROVED DRAFT LABELING


APPROVED
75 mg
(2 mg/mL)
Each mL contains: Doxorubicin HCl 2 mg, sodium chloride 0.9% and water for injection q.s.* Hydrochloric acid is used to adjust pH to a target of 3.0.
WARNING: Severe cellulitis, vesication and tissue necrosis will occur if doxorubicin HCl is extravasated during administration.
*Patent pending
75 mg
(2 mg/mL)
STERILE, ISOTONIC SOLUTION
FOR INTRAVENOUS USE ONLY
Store under refrigeration 2°-8°C (36°-46°F).
Protect from light. Retain in carton until time of use.
*Manufactured under process of U.S. Pat. 3,803,124.
CAUTION: Federal law prohibits dispensing without prescription.
37.5 mL SINGLE DOSE VIAL
75 mg
(2 mg/mL)
USUAL DOSAGE: Before administering, read package insert for complete prescribing and product information.
CONTAINS NO PRESERVATIVE—Discard unused portion.
JUL 9 1993
ADRIA LABORATORIES
COLUMBUS, OHIO 43216
75 mg
(2 mg/mL)
STERILE, ISOTONIC SOLUTION
FOR INTRAVENOUS USE ONLY
Store under refrigeration 2°-8°C (36°-46°F).
Protect from light. Retain in carton until time of use.
*Manufactured under process of U.S. Pat. 3,803,124.
CAUTION: Federal law prohibits dispensing without prescription.
37.5 mL SINGLE DOSE VIAL
Adria
059860393
Lot No./Expires

ADRIAMYCIN PFS®
(DOXORUBICIN HCl INJECTION, USP)
AADA 63-165
100 mg Vial Label
Part # 059940393

Each mL contains: Doxorubicin HCl 2 mg, sodium chloride 0.9% and water for injection q.s. Hydrochloric acid is used to adjust pH to a target of 3.0.

Store under refrigeration, 2°-8°C (36°-46°F).

Protect from light. Retain in carton until time of use.

USUAL DOSAGE: Before administering, read package insert for complete prescribing and product information.

NDC 0013-1177-88

ADRIAMYCIN PFS®
(DOXORUBICIN HYDROCHLORIDE INJECTION, USP)

100 mg
(2 mg/mL)

STERILE, ISOTONIC SOLUTION FOR INTRAVENOUS USE ONLY

CAUTION: Federal law prohibits dispensing without prescription.

50 mL SINGLE DOSE VIAL

059940393

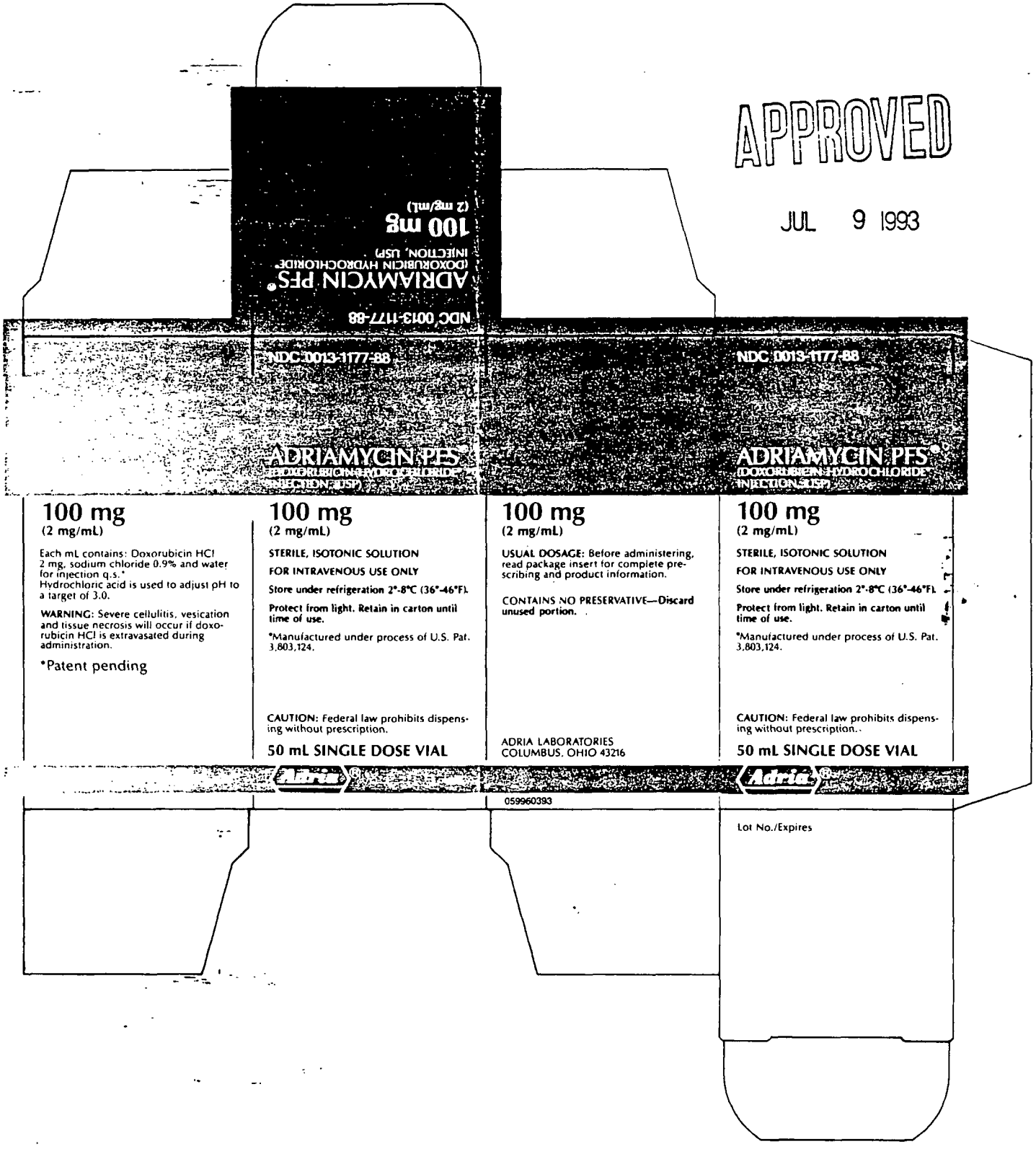
WARNING: Severe cellulitis, vesication and tissue necrosis will occur if doxorubicin HCl is extravasated during administration.

CONTAINS NO PRESERVATIVE – Discard unused portion.

ADRIA LABORATORIES
COLUMBUS, OHIO 43216

Lot No.:
Exp.:

APPROVED
JUL 9 1993



APPROVED

JUL 9 1993

NDC 0013-1177-88

ADRIAMYCIN PFS®
(DOXORUBICIN HYDROCHLORIDE)
INJECTION, USP

100 mg
(2 mg/mL)

NDC 0013-1177-88

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*Patent pending

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(2 mg/mL)

STERILE, ISOTONIC SOLUTION

FOR INTRAVENOUS USE ONLY

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Adria®

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CONTAINS NO PRESERVATIVE—Discard unused portion.

ADRIA LABORATORIES
COLUMBUS, OHIO 43216

059960393

NDC 0013-1177-88

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INJECTION, USP

100 mg
(2 mg/mL)

STERILE, ISOTONIC SOLUTION

FOR INTRAVENOUS USE ONLY

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CAUTION: Federal law prohibits dispensing without prescription.

50 mL SINGLE DOSE VIAL

Adria®

Lot No./Expires

Adria®

ADRIAMYCIN PFS®

(DOXORUBICIN HYDROCHLORIDE INJECTION, USP)

FOR INTRAVENOUS USE ONLY

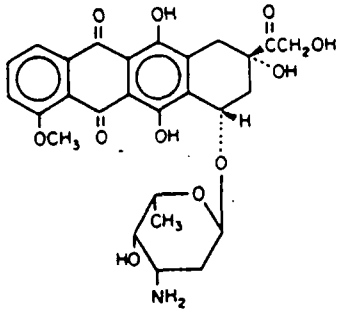
APPROVED
JUL 9 1993

059220393

WARNINGS

1. Severe local tissue necrosis will occur if there is extravasation during administration (See Dosage and Administration). ADRIAMYCIN PFS 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. ADRIAMYCIN PFS 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

.HCl

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.

ADRIAMYCIN PFS® (doxorubicin hydrochloride injection, USP) is a sterile, isotonic solution containing no preservative, for intravenous use only, available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg), 37.5 mL (75 mg), and 50 mL (100 mg) single dose vials and 100 mL (200 mg) multidose vial.

Each mL contains doxorubicin hydrochloride and the following inactive ingredients: sodium chloride 0.9% and water for injection q.s. Hydrochloric acid is used to adjust pH to a target pH of 3.0.

CLINICAL PHARMACOLOGY: Though not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind 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 the 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: ADRIAMYCIN® (Doxorubicin HCl, USP) 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.

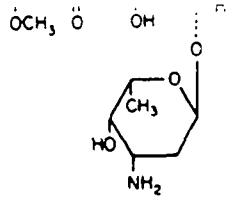
A number of other solid tumors have also shown some responsiveness but in numbers too limited to justify specific recommendation. Studies to date have shown malignant melanoma, kidney carcinoma, large bowel carcinoma, brain tumors and metastases to the central nervous system not to be significantly responsive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

CONTRAINDICATIONS: ADRIAMYCIN 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 ADRIAMYCIN 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 ADRIAMYCIN in such cases. ADRIAMYCIN treatment is contraindicated in patients who received previous treatment with complete cumulative doses of ADRIAMYCIN and/or daunorubicin.

WARNINGS: Special attention must be given to the cardiac toxicity exhibited by ADRIAMYCIN. 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 ADRIAMYCIN 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 ADRIAMYCIN therapy. Children appear to be at particular risk for development of delayed doxorubicin cardiotoxicity in that doxorubicin impairs myocardial growth as they mature, leading to possible subsequent development of congestive heart failure during early adulthood.

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/m² cummulative dose has been given is suggested. Transient EKG changes consisting of T-wave flattening, S-T depression and arrhythmias lasting for up to two weeks after a dose or course of ADRIAMYCIN are presently not considered indications for suspension of ADRIAMYCIN therapy. ADRIAMYCIN 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 ADRIAMYCIN. If test results indicate change in cardiac function associated with ADRIAMYCIN 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 ADRIAMYCIN administration.



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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 1000mm³ are to be expected during treatment with appropriate doses of ADRIAMYCIN. 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 ADRIAMYCIN therapy. Persistent severe myelosuppression may result in superinfection or hemorrhage.

ADRIAMYCIN 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 ADRIAMYCIN.

Toxicity to recommended doses of ADRIAMYCIN 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 ADRIAMYCIN given by i.v. push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

On intravenous administration of doxorubicin HCl 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.

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

Usage in Pregnancy—Safe use of ADRIAMYCIN in pregnancy has not been established. ADRIAMYCIN 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 ADRIAMYCIN 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, ADRIAMYCIN 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.

ADRIAMYCIN 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.

ADRIAMYCIN 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 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 ADRIAMYCIN 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 ADRIAMYCIN on three 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 non-lymphocytic leukemia treated with a 3-day course of ADRIAMYCIN 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 ADRIAMYCIN 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 with ADRIAMYCIN 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/m² 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 ADRIAMYCIN 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 ADRIAMYCIN, 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/m² 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/m² which has been reported to produce a lower incidence of congestive heart failure. Thirty (30) mg/m² on each of three successive days repeated every 4 weeks has also been used. ADRIAMYCIN 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.

It is recommended that ADRIAMYCIN PFS 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.

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

ADRIAMYCIN 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 ADRIAMYCIN PFS be mixed with other drugs.

ADRIAMYCIN 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 ADRIAMYCIN have been reported. Caution in the handling of the solution must be exercised and the use of gloves is recommended. If ADRIAMYCIN PFS 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.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED: ADRIAMYCIN PFS® (doxorubicin hydrochloride injection, USP)
Sterile, single use only, contains no preservative
NDC 0013-1136-91 10 mg vial, 2 mg/mL, 5 mL, 10 vial packs.
NDC 0013-1146-91 20 mg vial, 2 mg/mL, 10 mL, 10 vial packs.
NDC 0013-1156-79 50 mg vial, 2 mg/mL, 25 mL, single vial packs.
NDC 0013-1176-87 75 mg vial, 2 mg/mL, 37.5 mL, single vial packs.
NDC 0013-1177-88 100 mg vial, 2 mg/mL, 50 mL, single vial packs.

Store under refrigeration, 2°-8° C (36°-46° F). Protect from light and retain in carton until time of use. Discard unused solution.

Sterile, multidose vial, contains no preservative.
NDC 0013-1166-83 200 mg, 2 mg/mL, 100 mL multidose vial, single vial packs.

Store under refrigeration, 2°-8° C (36°-46°F). Protect from light and retain in carton until contents are used.

References

1. Rudolph R et al: Skin Ulcers Due to ADRIAMYCIN. Cancer 38:1087-1094, Sept. 1976.
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., Director of Pharmacy Services. Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.
5. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. Med J. Australia 1:426-428, 1983.
6. Jones R. et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. Ca—A Cancer Journal for Clinicians Sept/Oct, 258-263, 1983.
7. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic drugs in hospitals. Am J Hosp Pharm 47:1033-1049, 1990.
8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. AM J Hosp Pharm 1986; 43:1193-1204

extravasation have occurred. The injection [illegible]
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ADRIAMYCIN 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 ADRIAMYCIN have been reported. Caution in the handling of the solution must be exercised and the use of gloves is recommended. If ADRIAMYCIN PFS 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.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED: ADRIAMYCIN PFS® (doxorubicin hydrochloride injection, USP)
Sterile, single use only, contains no preservative
NDC 0013-1136-91 10 mg vial, 2 mg/mL, 5 mL, 10 vial packs.
NDC 0013-1146-91 20 mg vial, 2 mg/mL, 10 mL, 10 vial packs.
NDC 0013-1156-79 50 mg vial, 2 mg/mL, 25 mL, single vial packs.
NDC 0013-1176-87 75 mg vial, 2 mg/mL, 37.5 mL, single vial packs.
NDC 0013-1177-88 100 mg vial, 2 mg/mL, 50 mL, single vial packs.

Store under refrigeration, 2°-8° C (36°-46° F). Protect from light and retain in carton until time of use. Discard unused solution.

Sterile, multidose vial, contains no preservative.
NDC 0013-1166-83 200 mg, 2 mg/mL, 100 mL multidose vial, single vial packs.

Store under refrigeration, 2°-8° C (36°-46°F). Protect from light and retain in carton until contents are used.

References

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