Adriamycin RDF®
doxorubicin hydrochloride
for injection, USP

Adriamycin PFS®
doxorubicin hydrochloride
injection, USP

FOR INTRAVENOUS USE ONLY

WARNING
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. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may
occur either during therapy or months to years after termination of therapy. The probability of developing
impaired myocardial function based on a combined index of signs, symptoms and decline in left ventricular
ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m2 of doxorubicin,
2 to 5% at a dose of 400 mg/m2, 5 to 8% at 450 mg/m2, and 6 to 20% at 500 mg/m2.* The risk of developing
CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 450 mg/m2. This
toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent
cyclophosphamide therapy or with pre-existing heart disease. Pediatric patients are at increased risk for
developing delayed cardiotoxicity.
3. Dosage should be reduced in patients with impaired hepatic function.
4. Severe myelosuppression may occur.
5. Doxorubicin should not be administered in patients under the supervision of a physician who is experienced in the use
of cancer chemotherapeutic agents.

* Data on file at Pharmacia & Upjohn

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.
Chemically, doxorubicin hydrochloride is:
\[
\text{C}_{27}\text{H}_{29}\text{NOnO}_{11}\cdot\text{HCl} \quad \text{M.W.} = 579.99
\]
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.

ADRIAMYCIN RDF® (doxorubicin hydrochloride for injection, USP) a sterile red-orange lyophilized powder for
intravenous use only, is available in 10, 20 and 50 mg single dose vials and a 150 mg multidose vial.
Each 10 mg single dose vial contains 10 mg of doxorubicin HCI, USP, 50 mg of lactose, NF (hydrous) and 1 mg of
methylparaben, NF (added to enhance dissolution) as a sterile red-orange lyophilized powder.
Each 20 mg single dose vial contains 20 mg of doxorubicin HCI, USP, 100 mg of lactose, NF (hydrous) and 2 mg of
methylparaben, NF added to enhance dissolution as a sterile red-orange lyophilized powder.
Each 50 mg single dose vial contains 50 mg of doxorubicin HCI, USP, 250 mg of lactose, NF (hydrous) and 5 mg of
methylparaben, NF added to enhance dissolution as a sterile red-orange (lyophilized powder.
Each 150 mg multidose vial contains 150 mg of doxorubicin HCI, USP, 750 mg of lactose, NF (hydrous) and 15 mg of
methylparaben, NF added to enhance dissolution as a sterile red-orange (lyophilized powder.

ADRIAMYCIN PFS® (doxorubicin hydrochloride injection, USP) is a sterile parenteral, isotonic solution for intravenous
use only, containing no preservative, available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg), and 57.5 mL (75 mg)
single dose glass vials and a 100 mL multidose glass vial. ADRIAMYCIN PFS is also available in 5 mL (10 mg),
10 mL (20 mg), and 25 mL (50 mg) single dose Cytosafe™ vials and 75 mL (150 mg) and 100 mL (200 mg) multidose
Cytosafe vials.
Each mL contains doxorubicin HCI 2 mg, USP and the following inactive ingredients: sodium chloride 0.9% and
water for injection q.s. Hydrochloric acid is used to adjust the pH to a target pH of 3.0.

3. Secondary acute myelogenous leukemia (AML) has been reported in patients treated with anthracyclines, including doxorubicin (see ADVERSE REACTIONS). The occurrence of refractory secondary leukemia is more common when such drugs are given in
combination with DNA-damaging anti-neoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when
doses of anthracyclines have been escalated. The rate of developing treatment-related leukemia was estimated in an analysis of 1474
breast cancer patients who received adjuvant treatment with doxorubicin-containing regimens (i.e., FAC) in clinical trials. The
estimated risk of developing treatment-related leukemia at 10 years was 2.5% for the 810 patients receiving radiotherapy plus
chemotherapy and 0.5% for the 664 patients receiving chemotherapy alone. The overall risk was estimated at 1.5% at 10 years for
the entire patient population. Pediatric patients are also at risk of developing secondary AML.
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CLINICAL PHARMACOLOGY: The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Interception inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleaveable complexes appears to be an important mechanism of drug activity, which may contribute to the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

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, mucositis, and alopecia in all species and atrophy to testes in rats and dogs. Pharmacokinetic studies, determined in patients with various types of tumors undergoing either single or multi-agent therapy have shown that doxorubicin follows a multiphasic disposition after intravenous injection. The initial distribution half-life of approximately 5.0 minutes suggests rapid tissue uptake of doxorubicin, with its slow elimination from tissues is reflected by a terminal half-life of 20 to 48 hours. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. Approximately 40% of the drug appears in the urine, while only 5 to 12% of the drug and its metabolites appear in the urine during the one week period. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 70 to 75% and is independent of plasma concentration of doxorubicin up to 2 µM. Enzymatic reduction at the 7 position and cleavage of the daunosamine sugar yields aglycones which are accompanied by free radical formation, the local production of reactive species including the hydroxyl free radical OH•. Free radical formation has been implicated in doxorubicin cardiotoxicity. Disposition of doxorubicinol (DOX-OL) in patients is formation rate limited. The terminal half-life of DOX-OL is similar to doxorubicin. The relative exposure of DOX-OL compared to doxorubicin ranges between 0.4 to 0.6. In urine, <5% of the dose was recovered as DOX-OL over 7 days.

A published clinical study involving 6 men and 21 women with no prior anthracycline therapy reported a significantly higher median doxorubicin clearance in the men compared to the women (113 versus 45 L/hr). However, the terminal half-life of doxorubicin was longer in men compared to the women (44 versus 58 hrs.). In patients, dose-independent pharmacokinetics have been shown for doxorubicin in the dose range of 30 to 70 mg/m2. Systemic clearance of doxorubicin is significantly reduced in obese women with ideal body weight greater than 130%. There was a significant reduction in clearance without any change in volume of distribution in obese patients when compared with normal patients with less than 115% ideal body weight. The clearance of doxorubicin and doxorubicinol was also reduced in patients with impaired hepatic function. Doxorubicin was excreted in the milk of one lactating patient, with peak milk concentration at 24 hours after treatment being approximately 4.5-fold greater than the corresponding plasma concentration. Doxorubicin was detectable in the milk up to 72 hours after therapy with 70 mg/m2 of doxorubicin given as a 10 minute intravenous infusion and 100 mg/m2 of cisplatin as a 2-hour intravenous infusion. The peak concentration of doxorubicinol in milk at 24 hours was 0.2 µM and AUC up to 24 hours was 16.5 µM hr while the AUC for doxorubicin was 9.9 µM hr.

Following administration of 10 to 75 mg/m2 doses of doxorubicin to 60 children and adolescents ranging from 2 months to 20 years of age, doxorubicin clearance averaged 1443 ± 114 mL/min/m2. Further analysis demonstrated that clearance in 52 children greater than 2 years of age (1540 mL/min/m2) was increased compared with adults. However, clearance in infants younger than 2 years of age (815 mL/min/m2) was decreased compared with older children and approached the range of clearance values determined in adults.

Doxorubicin does not cross the blood brain barrier.

INDICATIONS AND USAGE: ADRIAMYCIN PFS and ADRIAMYCIN RDF have 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, gastric carcinoma, Hodgkin’s disease, malignant lymphoma and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types.

CONTRAINDICATIONS: Doxorubicin therapy should not be started in patients who have marked myelosuppression induced by previous treatment with other antitumor agents or by radiotherapy. Doxorubicin treatment is contraindicated in patients who received previous treatment with complete cumulative doses of doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracyclines.

WARNINGS: Special attention must be given to the cardiotoxicity induced by doxorubicin. Irreversible myocardial toxicity, manifested in its most severe form by life-threatening or fatal congestive heart failure, may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function, based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m2 of doxorubicin, 3 to 5% at a dose of 400 mg/m2, 5 to 8% at a dose of 450 mg/m2 and 6 to 20% at a dose of 500 mg/m2 given in a schedule of a bolus injection followed by 3 weeks. In a retrospective review by von Hoff et al, the probability of developing congestive heart failure was reported to be 5/168 (3%) at a cumulative dose of 430 mg/m2 of doxorubicin, 8/110 (7%) at 575 mg/m2 and 5/14 (36%) at 728 mg/m2. The cumulative incidence of CHF was 2.2%. In a prospective study of doxorubicin in combination with cyclophosphamide, fluorouracil and/or vincristine in patients with breast cancer or small cell lung cancer, the cumulative incidence of congestive heart failure was 5 to 6%. The probability of CHF at various cumulative doses of doxorubicin was 1.5% at 300 mg/m2; 4.9% at 400 mg/m2; 7.7% at 450 mg/m2 and 20.5% at 500 mg/m2.

Cardiotoxicity may occur at lower doses in patients with prior mediastinal irradiation, concurrent cyclophosphamide therapy exposure at an early age and advanced age. Data also suggest that pre-existing heart disease is a co-factor for increased risk of doxorubicin cardiotoxicity. In such cases, cardiotoxicity may occur at doses lower than the recommended cumulative dose of doxorubicin. Studies have suggested that concomitant administration of doxorubicin and calcium channel entry blockers may increase the risk of doxorubicin cardiotoxicity. The total dose of doxorubicin administered to the individual patient should also take into account previous or concurrent therapy with other cardiotoxicity-related compounds such as daunorubicin, idarubicin and mitoxantrone. Cardiomyopathy and/or congestive heart failure may be encountered several months or years after discontinuation of therapy.

The risk of congestive heart failure and other acute manifestations of doxorubicin cardiotoxicity in pediatric patients may be as much or lower than in adults. Pediatric patients appear to be at particular risk for developing delayed cardiac toxicity.
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toxicity in that doxorubicin induced cardiomyopathy impairs myocardial growth as pediatric patients mature, subsequently leading to possible development of congestive heart failure during early adulthood. As many as 40% of pediatric patients may have subclinical cardiac dysfunction and 5 to 10% of pediatric patients may develop congestive heart failure on long term follow-up. This late cardiac toxicity may be related to the dose of doxorubicin. The longer the length of follow-up the greater the increase in the detection rate.

Treatment of doxorubicin induced congestive heart failure includes the use of diuretics, diuretics, after load reducers such as angiotensin converting enzyme (ACE) inhibitors, low salt diet, and bed rest. Such intervention may relieve symptoms and improve the functional status of the patient.

Monitoring Cardiac Function
In adult patients severe cardiac toxicity may occur precipitously without antecedent ECG changes. Cardiomyopathy induced by anthracyclines is usually associated with very characteristic histopathologic changes on examination of endomyocardial biopsy (EM biopsy), and a decrease of left ventricular ejection fraction (LVEF), as measured by multi-gated radionuclide angiography (MUGA scan) and/or echocardiogram (ECHO), from pretreatment baseline values. However, it has not been demonstrated that monitoring of the ejection fraction will predict when individual patients are approaching their maximally tolerated cumulative dose of doxorubicin. Cardiac function should be carefully monitored during treatment to minimize the risk of cardiac toxicity. A baseline cardiac evaluation with an ECG, LVF, and/or an echocardiogram (ECHO) is recommended especially in patients with risk factors for increased cardiac toxicity (pre-existing heart disease, mediastinal irradiation, or concurrent cyclophosphamide therapy). Subsequent evaluations should be obtained at a cumulative dose of doxorubicin of at least 400 mg/m² and periodically thereafter during the course of therapy. Pediatric patients are at increased risk for developing delayed cardiotoxicity following doxorubicin administration and therefore a follow-up cardiac evaluation is recommended periodically to monitor for this delayed cardiotoxicity.

In adults, a 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of 45% or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function. In pediatric patients, deterioration in cardiac function following the completion of therapy with doxorubicin is indicated by a drop in fractional shortening (FS) by an absolute value of 10 percentile units or below 29%, and a decline in LVEF of 10 percentile units or an LVEF below 55%. In general, if test results indicate deterioration in cardiac function associated with doxorubicin, the benefit of continued therapy should be carefully evaluated against the risk of producing irreversible cardiac damage.

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

There is a high incidence of bone marrow depression, primarily of leukocytes, requiring careful hematologic monitoring. With the recommended dose schedule, leukopenia is usually transient, reaching its nadir 10 to 14 days after treatment with recovery usually occurring by the 21st day. White blood counts as low as 1000/mm³ are to be expected and appropriate doses of doxorubicin plus red cell and platelet transfusions have been reported.

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. Pediatric patients receiving concomitant doxorubicin and actinomycin-D have manifested acute “recall” pneumonitis at variable times after local radiation therapy.

Since metabolism and excretion of doxorubicin occurs predominantly by the hepatobiliary route, toxicity to recommended doses of doxorubicin can be enhanced by hepatic impairment; therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional laboratory tests such as SCOT, SGPT, alkaline phosphatase and bilirubin (see DOSAGE AND ADMINISTRATION).

Necrotizing colitis manifested by typhilitis (local inflammation), bloody stools and severe and sometimes fatal infections have been associated with a combination of doxorubicin given by i.v. push daily for 5 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, 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.

Pregnancy: Category D—Safe use of doxorubicin in pregnancy has not been established. Doxorubicin is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. There are no adequate and well-controlled studies in pregnant women. If doxorubicin is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

PRECAUTIONS:

General
Doxorubicin is not an anti-microbial agent.

Information for Patients
ADRIAMYCIN PFS and ADRIAMYCIN RDF impart a red coloration to the urine for 1 to 2 days after administration, and patients should be advised to expect this during active therapy.

Drug Interactions
Paclitaxel: Two published studies report that initial administration of paclitaxel infused over 24 hours followed by doxorubicin administered over 48 hours resulted in a significant decrease in doxorubicin clearance with more profound neutropenic and stomatitis episodes than the reverse sequence of administration.

Progestosterone: In a published study, progestosterone was given intravenously to patients with advanced malignancies (ECOG PS<2) at high doses (up to 10 g over 24 hours) concomitantly with a fixed doxorubicin dose (60 mg/m² via bolus). Enhanced doxorubicin-induced neutropenia and thrombocytopenia were observed.

Verapamil: A study of the effects of verapamil on the acute toxicity of doxorubicin in mice revealed higher initial peak concentrations of doxorubicin in the heart with a higher incidence and severity of degenerative changes in cardiac tissue resulting in a shorter survival.

Cyclosporine: The addition of cyclosporine to doxorubicin may result in increases in AUC for both doxorubicin and doxorubicinol possibly due to a decrease in clearance of parent drug and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and
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prolonged hematologic toxicity than doxorubicin alone. Coma and/or seizures have also been described.
Literature reports have also described the following drug interactions: phenobarbital increases the elimination of
doxorubicin, phenytoin levels may be decreased by doxorubicin, streptozocin (Zanosar®) may inhibit hepatic
metabolism of doxorubicin, and administration of live vaccines to immunosuppressed patients including those
undergoing cytotoxic chemotherapy may be hazardous.
Laboratory Tests

initial treatment with doxorubicin requires observation of the patient and periodic monitoring of complete blood
counts, hepatic function tests, and radionuclide left ventricular ejection fraction. (See WARNINGS).

Like other cytotoxic drugs, doxorubicin may induce “tumor lysis syndrome” and hyperuricemia in patients with
rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this
complication.

Carcinogenesis, Mutagenesis, Impairment of Fertility.
Formal long-term carcinogenicity studies have not been conducted with doxorubicin. Doxorubicin and related
compounds have not been shown to have mutagenic and carcinogenic properties when tested in experimental models
(including bacterial systems, mammalian cells in culture, and female Sprague-Dawley rats).
The possible adverse effect on fertility in males and females in humans or experimental animals have not been
adequately evaluated. Fetal toxicity was observed in rats and dogs;

Treatment-related acute myelogenous leukemia has been reported in patients treated with
doxorubicin-containing adjuvant chemotherapy regimes (see ADVERSE REACTIONS, Hematologic
subsection below).

WARNINGS

Nursing Mothers:
Because of the potential for serious adverse reactions in nursing infants from doxorubicin, mothers should be
advised to discontinue nursing during doxorubicin therapy.

Pediatric Use:
Pediatric patients are at increased risk for developing delayed cardiotoxicity. Follow-up cardiac evaluations are
recommended periodically to monitor for this delayed cardiotoxicity (see WARNINGS).

Doxorubicin, as a component of intensive chemotherapy regimens administered to pediatric patients, may
contribute to prepubertal growth failure. It may also contribute to gonadal impairment, which is usually temporary.

ADVERSE REACTIONS:

Cardiotoxicity - (see WARNINGS).

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

CutaneousODESAGE AND ADMINISTRATION:)

Gastrointestinal - Acute nausea and vomiting occurs frequently and may be severe. This may be alleviated by
antiemetic therapy. Mucositis (ostematitis 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 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
who received doxorubicin combined with cytarabine. Anorexia and diarrhea have been occasionally reported.

Vascular - Phlebitis 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 extravasation of doxorubicin occurs during
administration. Enanthematous streaking along the vein proximal to the site of injection had been reported (see
DOSAGE AND ADMINISTRATION).

Hematologic - The occurrence of secondary acute myeloid leukemia with or without a preleukemic phase has been
reported in patients concurrently treated with doxorubicin in association with DNA-damaging

antisecretory agents. Such cases could have a short (1-5 years) latency period. Pediatric patients are also at risk of
developing secondary acute myeloid leukemia.

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

Neurological - Peripheral neuropathy in the form of local-regional sensory and/or motor disturbances have been
reported in patients treated intra-arterially with doxorubicin, mostly in combination with cisplatin. Animal studies
have demonstrated seizures and coma in rodents and dogs treated with intra-cardiac doxorubicin. Seizures and coma
have been reported in patients treated with doxorubicin in combination with cisplatin or vincristine.

Other - Conjugated and lactation occur rarely.

OVERDOSE:

Acute overdosage with doxorubicin enhances the toxic effect of mucositis, leukopenia and toxicity. Treatment of

acute overdose consists of treatment of the severely myelosuppressed patient with hospitalization, antimicrobials, platelet transfusions and symptomatic treatment of mucositis. Use of hematopoietic growth factor (i.e., G-CSF, GM-CSF) may be considered.

The 150 mg ADRIAMYCIN RDF and the 75 mL and 100 mL (2 mg/mL) ADRIAMYCIN PFS vials are packaged as
multiple dose vials and caution should be exercised to prevent inadvertent overdose.

Cumulative dosage with doxorubicin increases the risk of cardiomyopathy and resultant congestive heart failure
(see WARNINGS). Treatment consists of vigorous management of congestive heart failure with digitalis
calculants, and after-load reducers such as ACE inhibitors.

DOSAGE AND ADMINISTRATION: Care in the administration of ADRIAMYCIN PFS and ADRIAMYCIN RDF will reduce
the chance of perivenous infiltration (see WARNINGS). It may also decrease the chance of local reactions such as

Insert the following sentence:

An analysis of 1474 breast cancer patients who received adjuvant doxorubicin treatment in clinical trials, showed a
10-year estimated risk of developing treatment-related leukemia at 2.5% (95% confidence interval [CI], 1.0% to
5.1%) for the 810 patients receiving radiotherapy plus chemotherapy and 0.5% (95% CI, 0.1% to 2.4%) for the 664
patients receiving chemotherapy alone. The overall risk was 1.5% (95% CI, 0.7% to 2.9%) at 10 years for the
entire patient population.
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urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying burning or stinging sensation, 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 extravasation is suspected, intermittent application of ice to the site for 15 min. q.i.d. x 3 days may be useful. The benefit of local administration of other drugs may not be clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.

The most commonly used dose schedule when used as a single agent is 60 to 75 mg/m^2 as a single intravenous injection administered at 21-day intervals. The lower dosage should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. ADRIAMYCIN PFS and ADRIAMYCIN RDF have 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. When used in combination with other chemotherapy drugs, the most commonly used dosage of doxorubicin is 40 to 60 mg/m^2 given as a single intravenous injection every 21 to 28 days. Doxorubicin dosage must be reduced in case of hyperbilirubinemia as follows:

<table>
<thead>
<tr>
<th>Plasma bilirubin concentration (mg/dL)</th>
<th>Dosage reduction (%)</th>
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<tbody>
<tr>
<td>1.3 – 3.0</td>
<td>50</td>
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<tr>
<td>3.1 – 5.0</td>
<td>75</td>
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Reconstitution Directions: ADRIAMYCIN RDF, 10 mg, 20 mg, 50 mg, and 150 mg vials should be reconstituted with 5 mL, 10 mL, 25 mL, and 75 mL, respectively, of Sodium Chloride Injection, USP (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 buildup. 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 7 days at room temperature and under normal room light (100 foot-candles) and 15 days under refrigeration (2º to 8ºC). It should be protected from exposure to sunlight. Discard any of the unused solution from the 10 mg, 20 mg, and 50 mg single dose vials. Unused solutions of the multiple dose vial remaining beyond the recommended storage times should be discarded.

It is recommended that ADRIAMYCIN PFS and ADRIAMYCIN RDF 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.
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HOW SUPPLIED:

ADRIAMYCIN PFS® Injection (doxorubicin hydrochloride injection, USP)

SINGLE DOSE GLASS VIALS:
Sterile single use only, contains no preservative.
NDC 0013-1156-91 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, 25 mL, single vial packs

Store refrigerated, 2º to 8ºC (36º to 46ºF). Protect from light. Retain in carton until time of use. Discard unused portion.

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

Store refrigerated, 2º to 8ºC (36º to 46ºF). Protect from light. Retain in carton until contents are used.

MANUFACTURERS:
Pharmacia & Upjohn S.p.A. SP Pharmaceuticals LLC
Milan, Italy Albuquerque, NM 87109, USA

HOW SUPPLIED:

ADRIAMYCIN PFS® (doxorubicin hydrochloride injection, USP)

SINGLE DOSE VIALS, in single Cytosafe™ vials:
Sterile single use only polypropylene vials, contains no preservative.
NDC 0013-1236-91 10 mg vial, 2 mg/mL, 5 mL
NDC 0013-1246-91 20 mg vial, 2 mg/mL, 10 mL
NDC 0013-1256-79 50 mg vial, 2 mg/mL, 25 mL

Store refrigerated, 2º to 8ºC (36º to 46ºF). Protect from light. Retain in carton until time of use. Discard unused portion.

MULTIDOSE VIALS, in Cytosafe™ vial packs:
Sterile multidose polypropylene vials, contains no preservative.
NDC 0013-1286-83 150 mg, 2 mg/mL, 75 mL
NDC 0013-1266-83 200 mg, 2 mg/mL, 100 mL

Store refrigerated, 2º to 8ºC (36º to 46ºF). Protect from light. Retain in carton until contents are used.

MANUFACTURER:
Pharmacia & Upjohn (Perth)
Pty Limited
Bentley, WA 6102, Australia

REFERENCES:
3. National Study Commission on Cytotoxic Exposure—Recommendations for Handling of Cytotoxic Agents. Available from Louis P. Jeffrey, SDO, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.

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/s/
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Richard Pazdur
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