DOXORUBICIN HYDROCHLORIDE INJECTION, USP
Rx only
FOR INTRAVENOUS USE ONLY

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: 5,12-Naphthacenedione, 10-[[3- amino-2,3,6- trideoxy-β-D-lyxopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride [25376-40-9]. The structural formula is as follows:

\[

c_7h_{12}n_2o_{16} + 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.

Doxorubicin hydrochloride injection is a sterile, isotoxic, preservative-free solution for intravenous use. It is available in 20 mg (10 mL) and 25 mL (50 mg) single-dose vials and 100 mL (200 mg) multiple-dose vials. Each mL contains: Doxorubicin hydrochloride 2 mg; sodium chloride 9 mg for isotonicity; Water for injection q.s.; Hydrochloric acid and sodium hydroxide may have been added for pH adjustment (2.5-4.5).

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 damage. Binding properties of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytotoxic activity.

Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generates highly reactive species including the hydroxyl free radical OH•. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level.

Cells treated with doxorubicin have been shown to manifest 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, myelosuppression in all species and atrophy to testes in rats and dogs.

Pharmacokinetics
Pharmacokinetic studies, determined in patients with various types of tumors undergoing either single or multagent therapy have shown that doxorubicin follows a multiphasic disposition after intravenous injection. In four patients, doxorubicin has demonstrated dose-independent pharmacokinetics in the dose range of 30 to 70 mg/m².

Distribution
The initial distribution half-life of approximately 5 minutes suggests rapid tissue uptake of doxorubicin, while its slow elimination from tissues is reflected by a terminal half-life of 20 to 48 hours. Steady-state distribution volume ranges from 809 to 1214 L/m² and is indicative of extensive drug uptake into tissues. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74% and 76% and is independent of plasma concentration of doxorubicin up to 1.1 mcg/mL.

Doxorubicin was excreted in the milk of one lactating patient, with peak milk concentrations at 24 hours after treatment being approximately 4.4-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 15-minute intravenous infusion and 100 mg/m² of cisplatin as a 26-hour infusion. The peak concentration of doxorubicin in milk at 24 hours was 0.11 mcg/mL, and AUC up to 24 hours was 9.3 mcg.h/mL while the AUC for doxorubicin was 5.4 mcg.h/mL. Doxorubicin does not cross the blood brain barrier.

Metabolism
Enzymatic reduction at the 7 position and cleavage of the sugar moieties which are accompanied by free radical formation, the local production of which may contribute to the toxicity of doxorubicin, is the major elimination route of doxorubicin (DOX-OL) in patients. The formation rate limited, with the terminal half-life of DOX-OL in patients estimated to be 3 days. The active exposure of DOX-OL, i.e., the ratio between the AUC of DOX-OL and the AUC of doxorubicin, compared to doxorubicin ranges to 0.4 and 0.6.

Excretion
Plasma clearance is in the range 324 to 809 mL/min/m² and is predominately by metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same period. In urine, <3% of the dose was recovered as DOX-OL over 7 days. Systemic clearance of doxorubicin is significantly reduced in women with ideal body weight greater than 130%. There was a significant reduction in clearance without any change in volume distribution in obese patients when compared with normal patients with less than 115% ideal body weight.

Pharmacokinetics in Special Populations
Pediatric
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 decreased in children greater than 5 years of age (1540 mL/min/m²) which was increased compared to adults. In children, doxorubicin concentrations younger than 2 years of age (813 mL/min/m²) was decreased compared with older children and approached the range of clearance values determined in adults.

Geriatric
While the pharmacokinetics of elderly subjects (>65 years of age) have been evaluated, no dosage adjustment is recommended based on age (see PRECAUTIONS, Geriatric Use).

Gender
A published clinical study involving 6 men and 21 women with no prior anthracycline therapy receiving doxorubicin did not show a gender difference in doxorubicin clearance in the men compared to the women (1088 mL/min/m² versus 433 mL/min/m²). However, the half-life of doxorubicin was longer in men compared to the women (54 versus 35 hours).

Race
The influence of race on the pharmacokinetics of doxorubicin has not been evaluated.

Hepatic Impairment
The clearance of doxorubicin and doxorubicinol was reduced in patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

Renal Impairment
The influence of renal function on the pharmacokinetics of doxorubicin has not been evaluated.

CLINICAL STUDIES
The effectiveness of doxorubicin-containing regimens in the adjuvant therapy of early breast cancer has primarily been established based on data collected in a meta-analysis published in 1984 by the Early Breast Cancer Trialists Collaborative Group (EBCTCG). The EBCTCG obtains primary data on all relevant studies, both published and unpublished, for early stage breast cancer and regularly updates these data. The principal endpoints for the adjuvant chemotherapy trials were disease-free survival (DFS) and overall survival (OS). The EBCTCG meta-analysis included comparisons of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) to no chemotherapy (CMF-placebo), and comparisons of doxorubicin-containing regimens with CMF as an active control (6 trials involving 17523 patients). The pooled estimates of DFS and OS from these trials were used to calculate the effect of CMF relative to no therapy. The hazard ratio for DFS for CMF compared to no chemotherapy was 0.76 (95% CI 0.71 to 0.82) and for OS was 0.86 (95% CI 0.80 to 0.93). Based on a conservative estimate of CMF effect (lower 22.75% hazard ratio limit of 70% were premenopausal and 30% were postmenopausal. At the time of the meta-analysis, 1745 first recurrences and 1348 deaths had occurred. Analyses demonstrated that doxorubicin-containing regimens retained at least 75% of the historical CMF adjuvant effect on DFS and are effective. The hazard ratio for DFS (dox:CMF) was 0.91 (95% CI 0.82 to 1.01) and for OS was 0.95 (95% CI 0.81 to 1.03). These results of these analyses for both DFS and OS are provided in Table 1 and Figures 1 and 2.

Table 1. Summary of Randomized Clinical Trials Comparing Doxorubicin-Containing Regimens Versus CMF in EBCTG Meta-Analyses

<table>
<thead>
<tr>
<th>Study (starting year)</th>
<th>Regimens</th>
<th>No. of Cycles</th>
<th>No. of Patients</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-15</td>
<td>AC</td>
<td>4</td>
<td>1567</td>
<td>0.83 (0.82 to 0.83)</td>
<td>0.87 (0.83 to 0.89)</td>
</tr>
<tr>
<td>SE Sweden</td>
<td>FAC</td>
<td>6</td>
<td>201</td>
<td>0.95 (0.82 to 0.98)</td>
<td>0.89 (0.82 to 0.96)</td>
</tr>
<tr>
<td>SE Sweden</td>
<td>FAC</td>
<td>6</td>
<td>268</td>
<td>0.95 (0.82 to 0.98)</td>
<td>0.89 (0.82 to 0.96)</td>
</tr>
<tr>
<td>SE Sweden</td>
<td>FAC</td>
<td>12</td>
<td>113</td>
<td>0.71 (0.49 to 0.95)</td>
<td>0.64 (0.41 to 0.90)</td>
</tr>
<tr>
<td>SE Sweden</td>
<td>FAC</td>
<td>6</td>
<td>21</td>
<td>0.59 (0.37 to 0.81)</td>
<td>0.61 (0.38 to 0.84)</td>
</tr>
<tr>
<td>SE Sweden</td>
<td>FAC</td>
<td>6</td>
<td>113</td>
<td>0.89 (0.71 to 1.12)</td>
<td>0.88 (0.71 to 1.12)</td>
</tr>
<tr>
<td>SE Sweden</td>
<td>FAC</td>
<td>6</td>
<td>22</td>
<td>0.91 (0.53 to 1.57)</td>
<td>0.93 (0.53 to 1.57)</td>
</tr>
<tr>
<td>SE Sweden</td>
<td>FAC</td>
<td>6</td>
<td>121</td>
<td>1.07 (0.73 to 1.55)</td>
<td>0.99 (0.64 to 1.54)</td>
</tr>
<tr>
<td>SE Sweden</td>
<td>FAC</td>
<td>8</td>
<td>124</td>
<td>0.81 (0.52 to 1.29)</td>
<td>0.73 (0.47 to 1.12)</td>
</tr>
<tr>
<td>Combined Studies</td>
<td>DOX</td>
<td>1560</td>
<td></td>
<td>0.82 (0.81 to 0.83)</td>
<td>0.81 (0.80 to 0.83)</td>
</tr>
</tbody>
</table>

Abbreviations: DFS = disease-free survival; OS = overall survival; AC = doxorubicin, cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; FACV = 5-fluorouracil, doxorubicin, cyclophosphamide, vincristine; FACV = 5-fluorouracil, doxorubicin, cyclophosphamide, vincristine, bleomycin, Adriamycin; C = cyclophosphamide; V = vincristine; D = doxorubicin.

INDICATIONS AND USAGE:
Doxorubicin has been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms’ tumor, osteogenic sarcoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder cancer, rhabdomyosarcoma, gastric carcinoma, Hodgkin’s disease, malignant lymphoma and bronchogenic carcinoma in which the small cell histologic type is the most prominent.

CONTRAINICATIONS:
Patients should not be treated with doxorubicin if they have any of the following conditions: baseline neutrophil count < 1500 cells/mL; severe hepatic impairment; recent myocardial infarction; severe myocardial insufficiency; severe arrhythmias; previous treatment with doxorubicin; peripheral neuropathy; any of its excipients, or other anthracenes or anthracenediones; or hypersensitivity to doxorubicin.

WARNINGS:
Doxorubicin should be administered only under the supervision of qualified personnel. The drug has been used in the treatment of a variety of malignancies, in doses ranging from 200 mg/m² to 1000 mg/m². The clinical use of doxorubicin is associated with a high incidence of dose-limiting toxicity of the drug.

Cardiac Function
Cardiotoxicity is a known risk of anthracycline treatment. Anthracycline-induced cardiotoxicity may be manifested by early (delayed) events. Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and electrocardiogram (ECG) abnormalities such as specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and atrioventricular block have also been reported. These effects do not usually predict delayed cardiotoxicity, which is essentially irreversible, is rarely of clinical importance, and are generally not considered an indication for the suspension of anthracycline treatment.

Dose-related cardiotoxicity usually develops late in the course of therapy with doxorubicin or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment, have also been observed. Cardiomyopathy is manifested by a reduction in ejection fraction (LVEF) that can occur with or without symptoms of heart failure (CHF) such as tachycardia, dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, peripheral edema, pleural effusion, and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening events such as acute myocardial infarction (AMI) are more common than specific T-Wave changes. Tachyarrhythmias, including premature ventricular contractions and atrioventricular block have also been reported. These effects do not usually predict delayed cardiotoxicity, which is essentially irreversible, is rarely of clinical importance, and are generally not considered an indication for the suspension of anthracycline treatment.

The probability of developing impaired myocardial function, based on a combined index of signs and symptoms, is low at 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 once every 3 weeks. In a retrospective study of doxorubicin in combination with cyclophosphamide, fluorouracil, and vincristine in patients with small cell lung cancer or breast cancer, the probability of surviving 4 years at dose levels of 500 mg/m² was 74%, 54%, and 77%, respectively. The risk of developing CHF increases rapidly with increased cumulative doses of doxorubicin in excess of 400 mg/m².

Cardiotoxicity may occur at lower doses in patients with congenital heart disease, mediastinal irradiation, concomitant use of other cardiotoxic drugs, or doxorubicin exposure at an early age, and anthracyclines should be carefully evaluated against the risk of developing irreversible cardiac damage. In such cases, cardiac toxicology monitoring at doses below the recommended cumulative dose of doxorubicin. Studies have suggested that concomitant administration of anthracyclines at low dose entry blockers may increase the risk of doxorubicin cardiotoxicity. The total dose of doxorubicin administered to an individual patient should also take into account previous or concomitant therapy with related compounds such as doxorubicin and mitoxantrone. Although not formally tested, it is probable that the toxicity of doxorubicin and other anthracyclines or antineoplastics is additive. Cardiomyopathy and/or congestive heart failure may be encountered several months or years after completion of doxorubicin therapy. The risk of acute manifestations of doxorubicin cardiotoxicity is increased in patients who are elderly, below the age of 20 years, or who were aged 50 or older had an increased risk of developing secondary AML or MDS.

Cardiac toxicity may occur at doses as low as 200 mg/m². The rate of developing secondary AML or MDS has been reported to be as high as 3% in patients treated with doxorubicin. The risk of developing secondary AML or MDS is increased with the use of doxorubicin in combination with other chemotherapeutic agents, such as cyclophosphamide, vincristine, and prednisone.

Monitoring Cardiac Function
The occurrence of a life-threatening cardiac impairment may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of therapy at the first evidence of impaired function. The preferred method for assessing cardiac function is determination of LVEF measured by multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). An ECHO may also be done. A baseline cardiac evaluation with a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiac toxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up. In patients with risk factors for increased cardiac toxicity, such as a history of anthracycline- or anthractane use, the monitoring of cardiac function must be particularly strict and the risk versus benefit of further treatment with doxorubicin in patients with impaired cardiac function must be carefully evaluated.

Endomyocardial biopsy is recognized as the most sensitive diagnostic tool to detect anthracycline-induced cardiomyopathy; however, this invasive procedure is only performed on a routine basis. ECG changes such as dysrhythmias, a reduction of the QRS voltage, or a prolongation beyond normal limits of the PR interval may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive method for monitoring for anthracycline-related cardiotoxicity.

Pediatric patients are at increased risk for doxorubicin 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 interval is indicative of doxorubicin cardiotoxicity. In pediatric patients, deterioration in cardiac function during or after the completion of therapy with doxorubicin may be associated with a dose-related shortening of cardiac function (FS) by an absolute value of ≥ 10 percent units or below 29%, and a decline in LVEF of > 10% at any interval of LVEF below 55%. In general, if test results indicate deterioration in cardiac function associated with doxorubicin, the patient should be carefully evaluated against the risk of producing irreversible cardiac damage. Acute life-threatening arrhythmias and cardiac arrest have been reported to occur during or within a few hours after doxorubicin administration.

Hematologic Toxicity
As with other cytotoxic agents, doxorubicin may produce myelosuppression. Myelosuppression requires careful monitoring, and differential WBC, red blood cell (RBC), and platelet counts should be assessed before and during each cycle of therapy with doxorubicin. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) are the predominant manifestations of doxorubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug. With the recommended dose schedule, leukopenia is usually transient, reaching its nadir to 14 days after treatment with recovery usually occurring by the 21st day. Thrombocytopenia may also occur. Clinical consequences of severe myelosuppression include hemorrhage, sepsis, sepsis, and tissue hypoxia, or death.

Secondary Leukemia
The occurrence of secondary AML or MDS has been reported most commonly in patients treated with chemotherapy containing containing anthracyclines (including doxorubicin) and DNA-damaging antineoplastic agents, in combination with radiotherapy. Patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. Such cases generally occur after the therapy is discontinued. The rate of developing secondary AML or MDS has been estimated in an analysis of 8656 patients with early breast cancer. Two studies conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), including NSABPB-15, Patients who received standard doses of doxorubicin and standard or escalated doses of cyclophosphamide (AC) adjuvant chemotherapy were followed for 61,810 patient years. Among 4483 such patients who received conventional doses of AC, 11 cases of AML or MDS were identified, for an incidence of 0.32% per 1000 patient years (95% CI 0.16 to 0.57) and a cumulative incidence at 5 years of 0.21% (95% CI 0.10 to 0.41). In another analysis of 1474 patients with breast cancer who received adjuvant treatment with doxorubicin-containing regimens conducted at the University of Texas M.D. Anderson Cancer Center, the incidence was estimated at 1.5% at 10 years. In patients who received regimens with higher cyclophosphamide dose intensity, doxorubicin, or who were aged 50 or older had an increased risk of developing secondary AML or MDS.

Pediatric patients are also at risk of developing secondary AML.

Effects at Site of Injection
Phlebitis or thrombophlebitis at the injection site (see Pharmacology). The addition of cyclosporine to doxorubicin may produce irreversible myocardial damage with treatment with doxorubicin, as well as a risk of treatment-related leukemia. Because doxorubicin may induce chromosomal damage in sperm, men undergoing treatment with doxorubicin should use effective contraceptive methods. Women treated with doxorubicin may develop irreversible amenorrhea, or premature menopause.

Drug Interactions
Doxorubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect the metabolism of doxorubicin. Therapies that may affect doxorubicin metabolism include chemotherapy, immunomodulators, immunosuppressants, pharmacokinetics, therapeutic efficacy, and/or toxicity. Interactions associated with doxorubicin are summarized in Table 4. The use of doxorubicin in combination with other cytoxic drugs.

Paclitaxel
There have been a number of reports in the literature that indicate that doxorubicin may be co-administered with paclitaxel. Two published studies report that initial administration of paclitaxel infused over 4 hours followed by doxorubicin administered over 48 hours resulted in a significant decrease in doxorubicin clearance with minor neutropenic and stomatitis episodes than the reverse sequence of administration. Paclitaxel

In a published study, progesterone was given intravenously to patients with advanced malignancies (ECOG PS<2) at 100 mg/day (90 mg over 4 hours) concomitantly with a fixed doxorubicin dose (60 mg/m²) via bolus injection. Enhanced doxorubicin cardiotoxicity 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 higher incidence and severity of degenerative changes in cardiac histology resulting in shorter survival.

Cyclosporine
The addition of cyclosporine to doxorubicin may result in increases in AUC for both doxorubicin and doxorubicin metabolites possibly due to a decrease in clearance of parent drug and a decrease in metabolism of doxorubicin. Literature reports...
suggest that adding cyclophosphamide to doxorubicin results in more profound and prolonged hematologic toxicity than doxorubicin alone. Cardiac complications have also been described.

Doxorubicin In a clinical study of women with metastatic breast cancer, the concurrent use of the cardiotoxic agent doxorubicin and cytosine arabinoside (Ara-C) was associated with a lower tumor response rate. Later initiation of deoxorozoxane (after administration of a cumulative dose of 300 mg/m² of doxorubicin had been given as a component of FAC) was not associated with a reduction in chemotherapy activity. Doxorubicin has been indicated for use in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and are continuing with doxorubicin therapy.

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

Doxorubicin results in more profound and prolonged hematologic toxicity than doxorubicin alone. Cardiac complications have also been described.

Cyclophosphamide The addition of cyclophosphamide to doxorubicin treatment does not affect doxorubicin, but may result in an increase in exposure to cyclophosphamide, a metabolite. Doxorubicin is only 5% of the cytotoxic activity of doxorubicin. Concurrent treatment with doxorubicin has been reported to exaggerate cyclophosphamide-induced hemorrhagic cysts. Acute myeloid leukemia has been reported as a second malignancy after treatment with doxorubicin and cyclophosphamide.

Literature reports have also described the following drug interactions:

Phenothiazines decrease the elimination of doxorubicin; phenytoin levels may be decreased

Cyclosporine may potentially induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia has been evidenced in men treated with doxorubicin, mainly in combination therapies. Men undergoing doxorubicin treatment should use effective contraceptive methods.

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ure (see WARNINGS). Treatment consists of vigorous management of congestive heart failure with digitalis preparations, diuretics, and after-load reducers such as ACE inhibitors.

**DOSAGE AND ADMINISTRATION:**

Care in the administration of doxorubicin will reduce the risk of extravasation injury (see WARNINGS). 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 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.d. x 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation are 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/m² 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.

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. When used in combination with other chemotherapy drugs, the most commonly used dosage of doxorubicin is 40 to 60 mg/m² given as a single intravenous injection every 21 to 28 days.

In a large randomized study (NSABP B-15) of patients with early breast cancer involving axillary lymph nodes (see CLINICAL PHARMACOLOGY, CLINICAL STUDIES, and ADVERSE REACTIONS), adverse reactions in patients with early breast cancer receiving Doxorubicin-Containing Adjuvant Therapy, the combination dosage regimen of AC (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m²) was administered intravenously on day 1 of each 21-day treatment cycle. Four cycles of treatment were administered.

**Dose Modifications:**

Patients in the NSABP B-15 study could have dose modifications of AC to 75% of the starting doses for neutropenic fever/infection. When necessary, dose modifications of AC to 75% of the starting doses for at least 5 days after each treatment.

Prior to administration, whenever solution and container permit, visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**Handling and Disposal:**

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all the procedures recommended in the guidelines are necessary or appropriate. However, given the toxic nature of this substance, the following protective recommendations are provided:

- Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling doxorubicin should wear protective clothing: gowns, gloves and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed, absorbent paper.
- All items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk waste-disposal bags for high-temperature incineration.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then rinsed with water.
- All cleaning materials should be disposed of as indicated previously.
- In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush.
- In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.
- Caregivers of pediatric patients receiving doxorubicin should be counseled to take precautions (such as wearing latex gloves) to prevent contact with the patient’s urine and other body fluids for at least 5 days after each treatment.

**HOW SUPPLIED:**

Doxorubicin Hydrochloride Injection, USP, 2 mg/mL, a sterile product which contains no preservatives, is available as follows:

<table>
<thead>
<tr>
<th>Product No.</th>
<th>NDC No.</th>
<th>Dosage</th>
<th>Concentration (mg/mL)</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>88305</td>
<td>63323-883-05</td>
<td>Doxorubicin hydrochloride</td>
<td>10 mg in a 5 mL single dose flip-top vial, packaged individually.</td>
<td></td>
</tr>
<tr>
<td>88310</td>
<td>63323-883-10</td>
<td>Doxorubicin hydrochloride</td>
<td>20 mg in a 10 mL single dose flip-top vial, packaged individually.</td>
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<tr>
<td>88330</td>
<td>63323-883-30</td>
<td>Doxorubicin hydrochloride</td>
<td>50 mg in a 25 mL single dose flip-top vial, packaged individually.</td>
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</tr>
<tr>
<td>100161</td>
<td>63323-101-61</td>
<td>Doxorubicin hydrochloride</td>
<td>200 mg in a 100 mL multi-dose vial, packaged individually.</td>
<td></td>
</tr>
</tbody>
</table>

Store refrigerated, 2° to 8°C (36° to 46°F).

**PROTECT FROM LIGHT:**

Retain vial in carton until time of use. Preserve Free. Discard unused portion.

Vial stoppers do not contain natural rubber latex.

**REFERENCES:**


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


