PRODUCT MONOGRAPH

[Pr]DOXORUBICIN

doxorubicin hydrochloride injection

Preservative-Free Solution

2 mg/mL

10 mg (5 mL), 50 mg (25 mL)
and 200 mg (100 mL) Vials

Antineoplastic agent

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doxorubicin hydrochloride injection

Preservative-Free Solution

PART I: HEALTH PROFESSIONAL INFORMATION

CAUTION:

DOXORUBICIN(DOXORUBICIN HYDROCHLORIDE) IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPY DRUGS (SEE **WARNINGS AND PRECAUTIONS**). BLOOD COUNTS AND HEPATIC FUNCTION TESTS SHOULD BE PERFORMED REGULARLY. BECAUSE OF THE EXPERIENCE WITH CARDIAC TOXICITY, IT IS NOT RECOMMENDED TO EXCEED A TOTAL DOSE OF DOXORUBICIN 550 MG/M^2 WITH THE 21-DAY REGIMEN AND 700 MG/M^2 WITH THE WEEKLY REGIMEN. CARDIAC MONITORING IS ADVISED IN THOSE PATIENTS WHO HAVE RECEIVED MEDIASTINAL RADIOTHERAPY, OTHER ANTHRACYCLINE OR ANTHRACENE THERAPY, WITH PRE-EXISTING CARDIAC DISEASE, OR WHO HAVE RECEIVED PRIOR DOXORUBICIN CUMULATIVE DOSES EXCEEDING 400 MG/M^2 WITH THE 21-DAY REGIMEN AND 550 MG/M^2 UTILIZING THE WEEKLY REGIMEN.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Parenteral and intravesical	Ready to use solution for injection 2 mg/mL (5mL, 25ml, 100mL vials)	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

DOXORUBICIN (doxorubicin hydrochloride) has been used successfully both as a single agent and also in combination with other approved cancer chemotherapeutic agents to produce regression in neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastomas, soft tissue sarcomas, bone sarcomas, breast carcinoma, gynecologic carcinomas, testicular carcinomas, bronchogenic carcinoma, Hodgkin's disease, non-Hodgkin's lymphoma, thyroid carcinoma, bladder carcinomas, squamous cell carcinoma of the head and neck, and gastric carcinoma.

DOXORUBICIN has also been used by instillation into the bladder for the topical treatment of superficial bladder tumors.

A number of other solid tumors have also shown some responsiveness to DOXORUBICIN alone or in combination with other drugs (see **DOSAGE AND ADMINISTRATION**). Studies to date have shown malignant melanoma, kidney carcinoma, large bowel carcinomas, brain tumors and metastases to the central nervous system not to be significantly responsive to DOXORUBICIN therapy.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Hypersensitivity to doxorubicin or any other component of the product, other anthracyclines or anthracenediones such as EPIRUBICIN (epirubicin hydrochloride), daunorubicin hydrochloride, mitoxantrone or mitomycin C.
- Marked persistent myelosuppression induced by prior treatment with other antitumor agents or by radiotherapy;
- Severe hepatic impairment;
- Severe myocardial insufficiency;
- Recent myocardial infarction;
- Severe arrhythmias;
- History of severe cardiac disease;
- Previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin and/or other anthracyclines and anthracenediones (see **WARNINGS AND PRECAUTIONS**).

Contraindication for intravesical use:

- Hematuria;
- Urinary tract infections;
- Inflammation of the bladder.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Doxorubicin should be administered only under the supervision of physicians experienced in the use of cytotoxic therapy (see **DOSAGE AND ADMINISTRATION**).

- Cardiomyopathy may develop during treatment or up to several years after completion of treatment and can include decrease in LVEF and signs and symptoms of congestive heart failure (CHF). The probability of developing cardiomyopathy is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m^2 of doxorubicin HCl, 3 to 5% at a dose of 400 mg/m^2, 5 to 8% at a dose of 450 mg/m^2, and 6 to 20% at a dose of 500 mg/m^2, when doxorubicin HCl is administered every 3 weeks. Thereafter, the risk of developing CHF increases steeply, and it is recommended not to exceed a maximum cumulative dose of 550 mg/m^2 (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

- Secondary Malignancies: Secondary leukemia has been reported in patients treated with anthracyclines, including doxorubicin. The risk of developing secondary acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) is increased following treatment with doxorubicin HCl. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, in combination with radiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. Cumulative incidences ranged from 0.2% at five years to 1.5% at 10 years in two separate trials involving the adjuvant treatment of women with breast cancer. These leukemias generally occur within 1 to 3 years of treatment (see **WARNINGS AND PRECAUTIONS, Secondary Malignancies**).

- Extravasation and Tissue Necrosis: Extravasation of doxorubicin during intravenous injection may produce local pain, severe tissue lesions (blistering, ulceration, vesication, severe cellulitis), and necrosis requiring wide excision of the affected area and skin grafting. Should signs or symptoms of extravasation occur, the drug infusion should be immediately stopped (see **WARNINGS AND PRECAUTIONS, Extravasation**).

- Myelosuppression and Sequelae: Doxorubicin can cause severe myelosuppression. Clinical consequences of severe myelosuppression include fever, infections (of bacterial, fungal or viral origin, e.g., sepsis/septicemia, lung infection, urinary tract infection), septic shock, hemorrhage, tissue hypoxia, or death (see **WARNINGS AND PRECAUTIONS, Hematologic**).

- Hepatic Impairment: The major route of elimination of doxorubicin is the hepatobiliary system. Patients with severe hepatic impairment should not receive doxorubicin. Obtain liver tests including SGOT, SGPT, alkaline phosphatase, and bilirubin prior to and during doxorubicin HCl therapy (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Doxorubicin was genotoxic in a battery of in vitro or in vivo tests. An increase in the incidence of mammary tumors was reported in rats, and a trend for delay or arrest of follicular maturation was seen in female dogs.

In women, doxorubicin may cause infertility during the time of drug administration. Doxorubicin may cause amenorrhea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.

Doxorubicin was toxic to male reproductive organs in animal studies, producing testicular atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia.

Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing doxorubicin treatment should use effective contraceptive methods.

Cardiovascular

Acute life-threatening arrhythmias have been reported to occur during or within a few hours after DOXORUBICIN (doxorubicin hydrochloride) administration (see **ADVERSE REACTIONS**).

Cardiac Function - Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e., acute) or late (i.e., delayed) events.

Early (i.e., Acute) Events –Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/ or ECG abnormalities such as non-specific ST-T wave changes.

Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, and atrioventricular and bundle-branch block also have been reported. Those effects usually do not predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance and generally do not necessitate discontinuation of doxorubicin treatment.

Late (i.e., Delayed) Events - Delayed 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 reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion and gallop rhythm. Subacute effects such as pericarditis/myocarditis also have been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and is the cumulative dose-limiting toxicity of anthracycline drugs.

The probability of developing CHF, estimated around 1% to 2% at a cumulative dose of 300 mg/m^2, slowly increases up to the total cumulative dose of 450 -550 mg/m^2. Thereafter, the risk of developing CHF increases steeply (3 to 5% at 400 mg/m^2; 5 to 8% at 450 mg/m^2, and 6 to 20% at 500 mg/m^2). **IT IS RECOMMENDED NOT TO EXCEED A MAXIMUM CUMULATIVE DOSE OF 550 MG/M^2 OF DOXORUBICIN.**

The total dose of DOXORUBICIN administered to a patient should take into account: prior therapy with related compounds such as epirubicin and daunorubicin or anthracene derivatives; and/or radiotherapy to the mediastinal area.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones and concomitant use of drugs with the ability to suppress cardiac contractility or cardiotoxic drugs. Anthracyclines including doxorubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored.

Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The reported half-life of trastuzumab is approximately 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Cardiac function must be carefully monitored in patients receiving high cumulative doses and in those with risk factors. While cardiotoxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present, it may be more likely to occur at lower cumulative doses in patients with these risk factors.

New studies show that children and adolescents are at an increased risk for developing delayed cardiotoxicity following doxorubicin administration (up to 15 years). Females may be at greater risk than males. Follow-up cardiac evaluations such as ECHO LVEF/MUGA are recommended periodically to monitor for this effect (see Monitoring and Laboratory Tests).

Vascular Effects

Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see **DOSAGE AND ADMINISTRATION).** As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal), have been coincidentally reported with the use of doxorubicin.

Extravasation

Extravasation of doxorubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately stopped.

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving doxorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Gastrointestinal

Doxorubicin is emetogenic. Mucositis/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

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 IV push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

Genitourinary

DOXORUBICIN may impart a red colouration to the urine for 1 to 2 days after administration and patients should be advised to expect this during active therapy.

Hematologic

As with other cytotoxic agents, doxorubicin can cause severe myelosuppression. Hematologic profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopenia and neutropenia generally reach the nadir between days 10 and 14 after drug administration; the WBC/neutrophil counts return to normal values in most cases by Day 21. Thrombocytopenia and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death. Hematologic toxicity may require dose reduction or suspension or delay of DOXORUBICIN therapy. Persistent severe myelosuppression may result in superinfection or hemorrhage.

In early breast cancer patient study (National Surgical Adjuvant Breast and Bowel Project B-15), the incidence of severe myelosuppression was: grade 4 leukopenia (0.3%), grade 3 leukopenia

(3%), and grade 4 thrombocytopenia (0.1%). A dose-dependent, reversible neutropenia is the predominant manifestation of hematologic toxicity from doxorubicin HCl. When doxorubicin HCl is administered every 21 days, the neutrophil count reaches its nadir 10 to 14 days after administration with recovery usually occurring by the 21st day. Anemia may also occur.

Secondary Malignancies

Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with topoisomerase-II inhibitors including the anthracyclines such as doxorubicin. Secondary leukemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents (0.5%) and/or in combination with radiotherapy (2.5 %) with a risk estimated at 1.5% at 10 years. Secondary leukemia can have a 1-3 year latency period, and can occur as late as 10 years following treatment.

Pediatric patients are also at risk of developing secondary AML.

Hepatic/Biliary/Pancreatic

Doxorubicin is extensively metabolized by the liver and its major route of elimination is the hepatobiliary system. Toxicity to recommended doses of DOXORUBICIN is enhanced by hepatic impairment, therefore, prior to the individual dosing and during treatment, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as AST, ALT, alkaline phosphatase and bilirubin. Patients with elevated bilirubin may experience slower clearance of doxorubicin with an increase in overall toxicity. Lower doses of doxorubicin are recommended in these patients (see **DOSAGE AND ADMINISTRATION**). Patients with severe hepatic impairment should not receive doxorubicin (see **CONTRAINDICATIONS**).

Toxicites With Co-Administration of Antineoplastic Agents

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 has been reported to be increased by the administration of DOXORUBICIN.

Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with doxorubicin.

Tumor-Lysis Syndrome

Doxorubicin may induce hyperuricemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells (tumor-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

Additional Warnings and Precautions for Other Routes of Administration

Intravesical Route of Administration

Administration of doxorubicin by the intravesical route may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, hematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterization problems (e.g., urethral obstruction due to massive intravesical tumors).

Special Populations

Pregnant Women:
The embryotoxic potential of doxorubicin was confirmed in vitro and in vivo. When given to female rats before and during mating, pregnancy, and lactation, doxorubicin was toxic to both dams and fetuses.

Doxorubicin has been implicated in causing fetal harm when administered to a pregnant woman. If a woman receives doxorubicin during pregnancy or becomes pregnant while taking the drug, she should be informed of the potential hazard to the fetus.

Nursing Women:
Doxorubicin is secreted into breast milk. Mothers should not breast-feed while undergoing chemotherapy with DOXORUBICIN.

Pediatric Population: Pediatric population is at a higher risk of Secondary Leukemia (AML included). Early and delayed cardiotoxicities have been described in children. On long-term follow-up, subclinical cardiac dysfunction may occur in over 20% of pediatric patients and 5% may develop congestive heart failure. This long-term cardiotoxicity may be related to the dose of doxorubicin.

Monitoring and Laboratory Tests

Initial treatment with DOXORUBICIN requires close observation of the patient and extensive laboratory monitoring. Like other cytotoxic drugs, DOXORUBICIN may induce hyperuricemia secondary to rapid lysis of neoplastic cells, particularly in patients with leukemia. The clinician should monitor the patient's serum chemistry and blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem. Hydration, urine alkalinization and allopurinol administration will help to prevent or minimize potential complications of tumor-lysis syndrome.

Hematologic profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts.

Evaluation of hepatic function is recommended using conventional clinical laboratory tests such as AST, ALT, alkaline phosphatase and bilirubin.

The systemic clearance of doxorubicin has been found to be reduced in obese patients (i.e., > 130% ideal body weight; see **DOSAGE AND ADMINISTRATION**, *Other Special Populations*).

Cardiac function should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher cumulative anthracycline doses (e.g. $\geq$ 450 mg/m^2). The technique used for assessment should be consistent throughout follow-up.

DOXORUBICIN is not an anti-microbial agent.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following adverse events have been reported in association with DOXORUBICIN (doxorubicin hydrochloride) therapy:

Cardiovascular:	sinus tachycardia, ECG abnormalities, tachyarrhythmias, atrio-ventricular and bundle branch block, asymptomatic reductions in left ventricular ejection fraction (LVEF), congestive heart failure, acute life-threatening arrhythmias during or within few hours after DOXORUBICIN administration [see **WARNINGS AND PRECAUTIONS, Cardiovascular: Maximum Cumulative Dose (550 mg/m^2)**)]
Hematologic:	leukopenia, neutropenia, anemia, thrombocytopenia, hemorrhage
Gastrointestinal:	anorexia, nausea/vomiting, dehydration, mucositis/stomatitis, hyperpigmentation of the oral mucosa, esophagitis, abdominal pain, gastric erosions, gastrointestinal tract bleeding, diarrhea, colitis
Liver:	changes in transaminase levels, hyperuricemia
Endocrine:	amenorrhea, hot flashes, oligospermia, azoospermia, weight gain
Ocular:	conjunctivitis/keratitis, lacrimation

Skin:	alopecia, local toxicity, rash/itch, skin changes, severe local tissue necrosis with intravenous injection, extravasation may occur, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin ('radiation recall reaction'), urticaria, acral erythema, palmar plantar erythrodysesthesia
Vascular:	phlebitis, thrombophlebitis, thromboembolism
Urological:	red coloration of urine for 1 to 2 days after administration
Bladder, local:	pain, hemorrhage, and occasionally decreased bladder capacity upon instillation
Local:	severe cellulitis, vesication, tissue necrosis upon extravasation, erythematous streaking along the vein proximal to the site of the injection (see **DOSAGE AND ADMINISTRATION**)
Other:	anaphylaxis, infection, sepsis/septicemia, acute lymphocytic leukemia, acute myelogenous leukemia, malaise/asthenia, fever, chills, shock, cross sensitivity to lincomycin

DRUG INTERACTIONS

DOXORUBICIN (doxorubicin hydrochloride) is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/hematologic and gastrointestinal effects (see **WARNINGS AND PRECAUTIONS**). The use of doxorubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment. Changes in hepatic function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

Literature reports have also described the following drug interactions:

- Paclitaxel can cause increased plasma-concentrations of doxorubicin and/or its metabolites when given prior to doxorubicin. The pharmacokinetic drug interaction is dependent on the administration schedule, dose, sequence, infusion duration and time interval between administration. Certain data indicate that this effect is minor when this anthracycline is administrated prior to paclitaxel;
- Phenobarbital increases elimination of doxorubicin;
- Phenytoin levels may be decreased by doxorubicin;
- Streptozocin may inhibit hepatic metabolism of doxorubicin;
- Exacerbation of cyclophosphamide induced hemorrhagic cystitis;
- Enhancement of the hepatotoxicity of 6-mercaptopurine;
- Concomitant actinomycin-D therapy produces "recall" acute pneumonitis at variable times after local radiation therapy, in pediatric populations;

- Increases in the AUC of doxorubicin as high as 47% were observed in concomitant treatments with sorafenib 400 mg twice daily. The clinical significance of these findings is unknown. Doxorubicin and sorafenib are not indicated for use in combination.
- Doxorubicin is a substrate of P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of P-gp (eg. verapamil), resulting in up to 2-fold higher doxorubicin plasma concentration and higher myelosuppression.
- Cyclosporine can cause an increased plasma concentration of doxorubicin and its active metabolite doxorubicinol by up to 55% and 443%, respectively possibly due to a decrease in clearance of the parent drug and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and prolonged hematologic toxicity than that observed with doxorubicin alone. Coma and seizures with fatal outcome have also been described with concomitant administration of cyclosporine and doxorubicin.

DOSAGE AND ADMINISTRATION

REFER TO SPECIAL HANDLING INSTRUCTIONS

Dosage

A variety of dose schedules has been used. The following recommendations are for use as a single agent only.

Intravenous (IV) Administration

The total DOXORUBICIN (doxorubicin hydrochloride) dose per cycle may differ according to its use within a specific treatment regimen (e.g., given as a single agent or in combination with other cytotoxic drugs) and according to the indication.

The most commonly used dosage schedule is 60-75 mg/m^2 as a single intravenous injection administered at 21-day intervals. An alternative dose schedule is weekly doses of 20 mg/m^2, which has been reported to produce a lower incidence of congestive heart failure. A dose of 30 mg/m^2 on each of 3 successive days repeated every 4 weeks has also been used.

Hepatic Dysfunction: DOXORUBICIN dosage must be reduced if the bilirubin is elevated as follows: Serum Bilirubin 1.2-3.0 mg/dL – give ½ of recommended starting dose, > 3 mg/dL – give ¼ of recommended starting dose. Doxorubicin should not be administered to patients with severe hepatic impairment (see **CONTRAINDICATIONS**).

Other Special Populations: Lower starting doses or longer intervals between cycles may need to be considered for heavily pretreated patients, children, elderly patients, obese patients, or patients with neoplastic bone marrow infiltration (see **WARNINGS AND PRECAUTIONS**).

Drug Incompatibility: Doxorubicin should not be mixed with fluorouracil (eg, in the same IV infusion bag or at the Y-site of an IV infusion line) since it has been reported that these drugs are

incompatible to the extent that a precipitate might form. If concomitant therapy with doxorubicin and fluorouracil is required, it is recommended that the IV line be flushed between the administration of these drugs.

Intravesical Administration

Intravesical administration is not suitable for the treatment of invasive tumors that have penetrated the muscular layer of the bladder wall. When DOXORUBICIN is instilled intravesically for the treatment of superficial bladder carcinomas, the usual dose employed ranges from 50-80 mg in a total volume of 50-100 mL of 0.9% Sodium Chloride Solution USP with a contact time of 1-2 hours. Care should be taken to ensure that the tip of the catheter is in the bladder cavity before instilling the DOXORUBICIN solution. Instillation is repeated weekly for 4 weeks, and subsequently at monthly intervals. Therapy may continue for 1 year or longer as no significant systemic toxicity has been reported. Care should be exercised in the handling and disposal of the voided urine. (Refer to **SPECIAL HANDLING INSTRUCTIONS.**) PVC gloves should be worn and the urine should be inactivated by decolorizing it with 10 mL or more of sodium hypochlorite solution (household bleach).

Other methods of administration have been investigated, including intra-arterial administration and also continuous or long-term intravenous infusion utilizing appropriate infusion pumps.

Clinical studies support the efficacy of DOXORUBICIN used concurrently with other chemotherapeutic agents. Listed below are tumor types and drugs used concurrently with DOXORUBICIN:

Acute lymphocytic leukemia in adults: DOXORUBICIN with vincristine and prednisone or with cytosine arabinoside, vincristine and prednisone.

Acute lymphocytic leukemia in children: DOXORUBICIN with L-asparaginase, vincristine and prednisone.

Acute non-lymphocytic leukemia: DOXORUBICIN with cytosine arabinosyl or with arabinosyl cytosine, vincristine and prednisone.

Carcinoma of the breast: DOXORUBICIN in treating early or advanced breast cancer in combination with 5-fluorouracil and/or cyclophosphamide or with vincristine with or without cyclophosphamide, or with taxane therapy.

Bronchogenic carcinoma, non-small cell: DOXORUBICIN with cyclophosphamide, methotrexate and procarbazine or with cyclophosphamide and cisplatinum.

Bronchogenic carcinoma, small cell: DOXORUBICIN with vincristine or etoposide (VP-16) and cyclophosphamide.

Hodgkin's disease: DOXORUBICIN with bleomycin, vincristine and dacarbazine.

Non-Hodgkin's lymphoma: DOXORUBICIN with cyclophosphamide, vincristine and prednisone, or bleomycin, cyclophosphamide, vincristine and prednisone.

Carcinoma of the ovary: DOXORUBICIN with cisplatinum.

Soft tissue sarcoma: DOXORUBICIN with dacarbazine, or with dacarbazine, cyclophosphamide and vincristine.

Carcinoma of the bladder: DOXORUBICIN with methotrexate, vinblastine and cisplatinum or cisplatinum and cyclophosphamide or with 5-fluorouracil.

Carcinoma of the stomach: DOXORUBICIN with 5-fluorouracil and mitomycin-C.

Administration

Intravenous (IV) Administration

Care in the administration of DOXORUBICIN 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 even if the 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, the following steps are recommended:

1. Attempt aspiration of the infiltrated DOXORUBICIN solution.

2. Local intermittent application of ice for up to 3 days.

3. Elevation of the affected limb.

4. Close observation of the lesion.

5. Consultation with a plastic surgeon familiar with drug extravasations if local pain persists or skin changes progress after 3 to 4 days. If ulceration begins, early wide excision of the involved area should be considered.

DOXORUBICIN should be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Solution USP (0.9%) or 5% Dextrose Solution USP. The tubing should be attached to a Butterfly needle, or other suitable device and 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 dosage should be administered for not less than 3 minutes and not more than 10 minutes to minimize the risk of thrombosis or perivenous extravasation. Local

erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration (see **WARNINGS AND PRECAUTIONS**).

Unless specific compatibility data are available, the mixing of DOXORUBICIN solutions with other drugs is not recommended. Precipitation occurs with 5-fluorouracil and heparin.

Intravesical Administration

Doxorubicin should be instilled using a catheter and retained intravesically for 1 to 2 hours. Care should be taken to ensure that the tip of the catheter is in the bladder cavity before instilling the DOXORUBICIN solution. During instillation, the patient should be rotated to ensure that the vesical mucosa of the pelvis receives the most extensive contact with the solution. To avoid dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. The patient should be instructed to void at the end of the instillation.

OVERDOSAGE

Acute overdosage with DOXORUBICIN (doxorubicin hydrochloride) 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Though not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind to DNA and inhibit nucleic acid synthesis.

Pharmacodynamics

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 wide 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 of testes in rats and dogs.

Pharmacokinetics

Pharmacokinetic studies show that the intravenous administration of normal or radiolabelled DOXORUBICIN (doxorubicin hydrochloride) for injection is followed by rapid plasma clearance and significant tissue binding. Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4-5% of the administered dose in 5 days. Biliary excretion represents the major excretion route, 40-50% 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.

STORAGE AND STABILITY

Store under refrigeration (2-8^{o}C), protect from light and retain in carton until time of use. Discard unused solution.

Storage of the solution for injection at refrigerated conditions can result in the formation of a gelled product. This gelled product will likely return to a slightly viscous to a mobile solution after 2 hours to a maximum of 4 hours equilibration at controlled room temperature (15-25°C)

Dispensing from the Pharmacy Bulk Vial should be completed within 8 hours of initial entry because of the potential for microbial contamination. The contents of the syringes filled from the Pharmacy Bulk Vial should be used within 24 hours at room temperature or 48 hours when refrigerated from the time of the initial entry into the Pharmacy Bulk Vial.

SPECIAL HANDLING INSTRUCTIONS

Preparation and Handling

1. Personnel should be trained in good techniques for reconstitution and handling. Pregnant staff should be excluded from working with this drug.

2. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II). The work surface should be protected by disposable, plastic-backed absorbent paper.

3. Personnel handling DOXORUBICIN (doxorubicin hydrochloride) solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks. If DOXORUBICIN contacts the skin or mucosa, the area should be washed with soap and water or sodium bicarbonate immediately. Do not abrade the skin by using a scrub brush and always wash hands after removing gloves.

4. In case of contact with the eye(s), hold back the eyelid of the affected eye(s) and flush with copious amounts of water for at least 15 minutes; proceed to a physician for medical evaluation.

5. Personnel regularly involved in the preparation and handling of antineoplastics should have blood examinations on a regular basis.

6. Directions for Dispensing from Pharmacy Bulk Vial

   The use of Pharmacy Bulk Vials is restricted to hospitals with a recognized intravenous admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for intravenous use only.

   Entry into the vial must be made with a suitable, sterile transfer or dispensing device. Multiple use of a syringe with needle is not recommended since it may cause leakage as well as increasing the potential for microbial and particulate contamination.

   In a suitable work area such as a laminar flow hood, swab the vial stopper with an antiseptic solution. Insert the device into the vial. Withdraw contents of the vial into sterile syringes using strict aseptic techniques. Dispensing from the Pharmacy Bulk Vial should be completed within 8 hours of the initial entry because of the potential for microbial contamination. Discard any unused portion. The contents of the syringes filled from the Pharmacy Bulk Vial should be used within 24 hours at room temperature or 48 hours when refrigerated from the time of the initial entry into the Pharmacy Bulk Vial.

Disposal

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.

2. All needles, syringes, vials and other materials which have come in contact with doxorubicin should be segregated in plastic bags, sealed, and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.

3. If incineration is not available, DOXORUBICIN may be detoxified by adding sodium hypochlorite solution (household bleach) to the vial, in sufficient quantity to decolorize the doxorubicin, care being taken to vent the vial to avoid a pressure build-up of the chlorine gas which is generated. Dispose of detoxified vials in a safe manner.

Needles, Syringes, Disposable and Non-disposable Equipment:

Rinse equipment with an appropriate quantity of sodium hypochlorite solution. Discard the solution and disposable equipment in a safe manner. Thoroughly wash non-disposable equipment in soap and water.

Spillage/Contamination:

Wear gloves, mask, protective clothing. Treat spilled powder or liquid with dilute sodium hypochlorite solution (1% available chlorine). Carefully absorb solution with gauze pads or towels, wash area with water and absorb with gauze or towels again and place in polyethylene bag; seal, double bag and mark as hazardous waste. Dispose of waste by incineration or by other methods approved for hazardous materials. Personnel involved in clean-up should wash with soap and water.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DOXORUBICIN (doxorubicin hydrochloride injection) is a sterile, isotonic, non-preserved solution, containing sodium chloride. The pH of the solution is adjusted by hydrochloric acid to a range of 2.5-3.5. It is supplied in glass or polypropylene vials as a 2 mg/mL sterile, isotonic, non-preserved solution.

10 mg (5mL) Glass Vials or Polypropylene Vials (supplied in a single vial per carton)
Each vial contains 10 mg of Doxorubicin Hydrochloride USP, 45 mg of Sodium Chloride USP, Water for Injection USP and Hydrochloric Acid USP for pH adjustment.

50 mg (25mL) Glass Vials or Polypropylene Vials (supplied in a single vial per carton)
Each vial contains 50 mg of Doxorubicin Hydrochloride USP, 225 mg of Sodium Chloride USP, Water for Injection USP and Hydrochloric Acid USP for pH adjustment.

200 mg (100 mL) Pharmacy Bulk Glass Vials or Polypropylene Vials (supplied in a single vial per carton)
Each vial contains 200 mg of Doxorubicin Hydrochloride USP, 900 mg of Sodium Chloride USP, Water for Injection USP and Hydrochloric Acid USP for pH adjustment.

NOTE: THE USE OF PHARMACY BULK VIALS IS RESTRICTED TO HOSPITALS WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM. THE PHARMACY BULK VIAL IS INTENDED FOR SINGLE PUNCTURE, MULTIPLE DISPENSING AND FOR INTRAVENOUS USE ONLY.

Incompatibility:

Unless specific compatibility data are available, DOXORUBICIN should not be mixed with other drugs. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin. Doxorubicin should not be mixed with heparin due to chemical incompatibility that may lead to precipitation. Precipitation also occurs with 5-fluorouracil.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

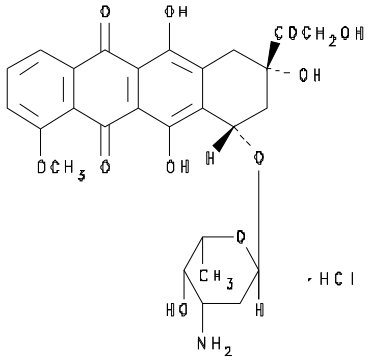
Drug Substance

Proper name: Doxorubicin Hydrochloride

Chemical name: (8S:10S)-10[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride(USAN).

Molecular formula and molecular mass: $C_{27}H_{29}NO_{11}.HCl$; 579.98

Structural formula:



Physicochemical properties: Doxorubicin hydrochloride is the hydrochloric acid salt of a glycoside antibiotic produced by *S. peucetius var. caesius*. It is a red-orange, almost odourless, hygroscopic powder, m.p. 205°C (dec.), $[\alpha]_D^{20}$ + 248°(c = 0.1 methanol), and soluble in water and dilute alcohols.

CLINICAL TRIALS

Clinical studies have shown a wide spectrum of antitumor activity in solid tumor and hematologic malignancies in adults and children when used as a single cytotoxic agent or in polydrug regimens. The most important therapeutic results achieved with DOXORUBICIN (doxorubicin hydrochloride) in the treatment of various malignancies are briefly summarized below:

Complete remission rates (CR), have been reported with doxorubicin when administered as single cytotoxic agent: 38% in sarcomas, about 40% in endometrial cancer, only poor results (15-

20%) in lung cancer depending on cell type, 5-8% in oesophageal cancer, 22-25% in cancer of the stomach, 25% in hepatocellular carcinoma, less than 5% in colo-rectal cancer and 8-10% in cancer of the pancreas. In thyroid carcinomas, doxorubicin alone gives an overall objective response rate of approximately 30%, in squamous cancers of the head and neck an overall response rate of about 20%.

In general, DOXORUBICIN gave higher CR and objective response rates in anthracycline-sensitive carcinomas when used in combination with other antitumor agents such as cyclophosphamide, corticosteroids (prednisone and dexamethasone), bleomycin, vinblastine, dacarbazine, methotrexate, vincristine, fluorouracil, platinum, etoposide, taxanes, actinomycin d, nitrosoures derivatives, mitomycin C and hydroxyurae.

DOXORUBICIN-containing regimen have drastically improved the CR rate up to about 75% in Hodgkin's disease, 60-82% in acute myeloblastic leukemia, and 70-80% in breast cancer.

To minimize cardiac toxicity of DOXORUBICIN, it is reported that equal low-dose (20 mg/m^2) weekly therapy is less cardiotoxic than high-dose (60-75 mg/m^2) therapy given every 3 weeks. These findings have also been confirmed when DOXORUBICIN is given in combination with other drugs. The total dose of DOXORUBICIN administered to a patient should take into account: prior therapy with related compounds such as epirubicin and daunorubicin or anthracene derivatives; and/or radiotherapy to the mediastinal area. Most important, it is recommended not to exceed a maximum cumulative dose of 550 mg/m^2 of DOXORUBICIN, with close monitoring of cardiac function in patients receiving a cumulative dose greater than 450 mg/m^2 (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**).

DETAILED PHARMACOLOGY

Doxorubicin, when administered IV, is rapidly cleared from the plasma of rodents, with concentration of the drug being seen in the liver, spleen, kidney, lung and heart. Drug excretion is prolonged and occurs predominantly via the liver.

In man, doxorubicin has also been shown to have a rapid plasma clearance and a large volume of distribution that suggests an extensive drug distribution into the tissues. Urinary excretion is minimal, with only 5% of the drug excreted during the first 5 days as measured by fluorimetric methods, suggesting prolonged tissue binding. After an injection of 1.5 mg/kg of tritium-labelled doxorubicin, approximately 50% of the administered radioactivity was detected in the feces in 7 days, while in patients with impaired liver function, the fecal excretion accounted for only 20%. Doxorubicin is metabolized predominantly by the liver to adriamycinol and several aglycone derivatives; approximately half of the drug excreted in bile was unchanged doxorubicin and 30% conjugates. Biliary excretion of doxorubicin was measured in 1 patient. A total of 40% of the administered dose was recovered as fluorescent material in the bile over a 1-week period.

The predominant fluorescent material in both urine and bile was doxorubicin followed by adriamycinol. Pharmacokinetic studies in patients with hepatic dysfunction show significant and prolonged plasma levels of doxorubicin metabolites associated with exaggerated clinical cytotoxicity. These observations are the basis of a requirement for dose de-escalation in patients with impaired hepatic function.

Neither doxorubicin nor any of its fluorescent metabolites were detectable in human cerebrospinal fluid obtained at varying intervals after drug administration in a variety of patients, including some with meningeal leukemia and cerebral metastasis, situations in which the blood brain barrier might be expected to be altered.

TOXICOLOGY

The acute toxicity of doxorubicin in Swiss mice varies greatly according to the route of administration. The LD_{50} is 8.5 mg/kg by the intra-peritoneal route, 21.1 mg/kg by the intravenous route, and greater than 750 mg/kg by the oral route.

Chronic toxicity was studied in the rabbit and in the dog. Doxorubicin when administered IV for three months at a daily dose of 0.125 mg/kg of body weight did not cause mortality or any measurable morphologic and functional changes in either species. At a dose of 0.25 mg/kg/day a few lesions were observed in the rabbit and more serious lesions in the dog, where the mortality rate reached 30%. The 0.5 mg/kg/day dose produced death in 40% of the treated rabbits within 2 months, and in 100% of the treated dogs within 10 days. Organs affected were gastrointestinal mucosa, hemopoietic tissues, and testes in both species, kidneys in the rabbit and skin (alopecia and melanosis) in the dog.

Teratology

Doxorubicin, when administered intravenously to rats at doses of 0.8 mg/kg/day during the period of organogenesis, resulted in an increased incidence of fetal resorption and fetal skeletal and soft tissue malformations. Rats treated intraperitoneally with doses of 1 mg/kg/day or greater also demonstrated skeletal and soft tissue malformations. The intravenous administration of doxorubicin to rabbits at doses of 0.1 mg/kg/day interfered with implantation and caused fetal resorption and at doses of 0.6 mg/kg/day was abortifacient. In addition, high single doses of 2 or 4 mg/kg in rabbits were shown to block implantation when administered on Day 3 of pregnancy, to be embryotoxic when administered on Day 7 of pregnancy, and to be abortifacient when administered on Days 11, 15 or 20 of pregnancy.

Carcinogenicity

Doxorubicin has been shown to be carcinogenic in the rat. The drug caused the appearance of breast fibroadenomas after a single IV dose of 8.0 mg/kg at an average of 33 weeks in 6 of 25 animals. Another animal developed a breast adenocarcinoma.

General

DOXORUBICIN was compared to the regular DOXORUBICIN lyophilized formulation administered IP in P388 leukemic mice and IV to Gross leukemic mice. No difference in activity or toxicity was noted between the 2 formulations.

In local tolerance studies conducted in mice, rats, rabbits, and dogs, either by the intravenous or intradermal routes, the lesions induced by the DOXORUBICIN formulation appeared to be similar to those obtained with the DOXORUBICIN lyophilized formulation. In other tests using DOXORUBICIN, there was no evidence of incompatibility with human blood, plasma or serum.

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PART III: CONSUMER INFORMATION

DOXORUBICIN
Doxorubicin hydrochloride injection

This leaflet is part III of a three-part "Product Monograph" published when DOXORUBICIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DOXORUBICIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
DOXORUBICIN is used alone and in combination with other anti-cancer medication to produce regression of tumor in several cancer conditions.

For the treatment of superficial bladder tumor, DOXORUBICIN is administered directly in the bladder.

What it does:
DOXORUBICIN is a chemotherapy drug, often used in combination with other drugs to kill cancer cells. Most chemotherapy agents (including DOXORUBICIN) work by killing rapidly dividing cells, such as cancer cells. This action can affect normal cells as well.

When it should not be used:

For intravenous administration:
- Allergy to doxorubicin hydrochloride or to any ingredient in the formulation or component of the container of DOXORUBICIN;
- Allergy to other anthracyclines or anthracenediones such as epirubicin hydrochloride, daunorubicin hydrochloride, mitoxantrone or mitomycin C;
- Persistent low blood cell count (myelosuppression);
- Severe liver disease;
- Severe heart disease;
- Recent heart attack;
- Severe irregular heartbeat;
- History of severe cardiac disease;
- Previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin and/or other anthracyclines and anthracenediones. Accumulation of anthracycline doses may be harmful for your heart.

For intravesical administration:
- Blood in urine;
- Urinary tract infections;
- Inflammation of the bladder.

What the medicinal ingredient is:
Doxorubicin hydrochloride.

What the important non-medicinal ingredients are:
Sodium Chloride USP,
Water for Injection USP and
Hydrochloric Acid USP for pH adjustment.

What dosage form it comes in:
DOXORUBICIN injection 2 mg/mL (doxorubicin hydrochloride injection) is available in 10 mg (5mL), 50 mg (25mL) and 200 mg (100mL) contained in glass or cytosafe (polypropylene) vials.

WARNINGS AND PRECAUTIONS

If you are prescribed DOXORUBICIN it will only be given to you by doctors or nurses experienced in giving chemotherapy.

If you take DOXORUBICIN you may get:

- **Damage to the heart muscle called heart failure. It is a decreased ability of the heart muscle to pump properly. This can lead to shortness of breath, swelling of the legs, irregular heart beat and sudden death. You are more likely to develop this as the dose is increased. It may occur during treatment or up to several years later.**
- **Risk of new cancers. You are at increased risk for getting certain blood cancers. They are called acute secondary myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). This can happen 1 to 3 years after treatment with DOXORUBICIN. It is more common if you take it at higher doses or with other cancer treatments. This risk also applies to children.**
- **Tissue damage. DOXORUBICIN will cause damage if it leaks out of your vein underneath your skin. You may get blisters or sores that require skin grafts. If it hurts, burns or sting in or around the vein into which the drug is being injected, tell the doctor or nurse IMMEDIATELY.**
- **Low blood cell counts. DOXORUBICIN can cause a severe decrease in the number of white blood cells, red blood cells, and platelets. This means that you may bruise or bleed more easily, go into shock and need blood transfusions.You may get fever, serious infection, and need treatment in a hospital. Low blood cell counts can lead to death. Your doctor will check your blood cell counts during your treatment and after you stop it. Call your doctor right away if you get severe bleeding, fever or chills with shivering.**
- **Risk of liver problems. Tell your doctor if you have a history of liver disease. You should not take DOXORUBICIN if you have a severe liver disease.**

BEFORE you use DOXORUBICIN talk to your doctor or pharmacist if:

- you have low blood cell counts;
- you have a liver disease;
- you have a heart disease, recent heart attack or irregular heartbeat;
- you are taking other drugs (including calcium channel blockers) or have been previously treated with DOXORUBICIN or other anti-cancer drugs, including anthracyclines (cardiotoxic drugs);
- you are pregnant, breast-feeding or planning to become pregnant.

As DOXORUBICIN may be harmful to an unborn child, women should be advised to avoid becoming pregnant. Effective contraceptive methods should be used.

As DOXORUBICIN may cause fertility impairment and damage chromosomes in sperm, men undergoing treatment with DOXORUBICIN should use effective contraceptive methods.

INTERACTIONS WITH THIS MEDICATION

Combination chemotherapy regimens that contain other agents with similar action may lead to additive toxicity, especially with regard to bone marrow/hematologic, gastrointestinal, and cardiac effects.

Administration of live vaccines to immunosuppressed patients including those undergoing cytotoxic chemotherapy should be avoided.

Drug interactions with DOXORUBICIN and the following drugs have been reported in the literature:

- Paclitaxel;
- Phenobarbital;
- Phenytoin;
- Streptozocin;
- Cyclophosphamide;
- Cyclosporine
- 6-mercaptopurine;
- Actinomycin-D.

PROPER USE OF THIS MEDICATION

How is DOXORUBICIN given?
You may receive DOXORUBICIN through a vein in the arm ("intravenously" or "IV") by your doctor or nurse, usually in the hospital, outpatient department or clinic.

If you are getting many injections over several weeks or months, for your convenience, your doctor may insert a catheter (thin tube) or port into a large vein in your body that is placed there as long as it is needed. Medicines get injected through the catheter or port rather than directly into a vein.

Depending on your medical condition, you may also receive DOXORUBICIN by instillation into your bladder through a catheter inserted into the urinary natural tract.

How much time does it take to get a treatment with DOXORUBICIN?
It usually takes about 3-10 minutes to inject DOXORUBICIN. However, you may get other medicines before or after DOXORUBICIN, so your entire treatment may last an hour or longer.

If you are administered DOXORUBICIN by instillation into your bladder, the solution should generally be retained in your bladder for 1-2 hours prior to voiding.

How long will I need treatment?
Your doctor will determine the length of your treatment based on your medical condition, your treatment goals, the medicines you receive, and how your body responds to those medicines.

Chemotherapy is usually given in cycles that include rest periods between treatments. The rest periods give your body a chance to build healthy new cells and regain your strength before your next treatment. DOXORUBICIN is usually given in treatment cycles of 21 days or 28 days. You may receive 1 dose of DOXORUBICIN every 3 or 4 weeks (on Day 1 of the cycle). Alternately, you may also receive DOXORUBICIN instilled into your bladder weekly for 4 weeks and then monthly. Your treatment cycle will depend on your medical condition and the other chemotherapy medicines you are getting.

Will I be able to work?
Some people work full time, while others work part time or wait until their chemotherapy treatments are finished. It depends on the type of job you have and the side effects you experience.

Is it okay to become pregnant or nurse a baby?
No. DOXORUBICIN can be harmful to an unborn child. If there is any possibility that you may become pregnant, ask your doctor about using birth control to prevent pregnancy during your treatment with DOXORUBICIN. Tell your doctor right away if you become pregnant during treatment. If you have been nursing, you should stop before starting treatment with DOXORUBICIN. Ask your baby's doctor to recommend a formula that would be best for your baby.

What should men consider when taking* DOXORUBICIN*?
Men undergoing treatment with doxorubicin should use effective contraceptive methods.

What happens after treatment?
After you have completed all your chemotherapy treatments, your doctor will check you regularly to make sure the cancer has not returned.

Overdosage:

If you think you have been given more DOXORUBICIN than you should, contact your doctor, nurse, or poison control centre immediately.

Missed Dose:
If you miss your scheduled treatment with the drug, contact your doctor as soon as possible to schedule your next treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, DOXORUBICIN can have side effects.

Common side effects include:
- hair loss, which is temporary and usually starts to grow back within 2 or 3 months after you have finished your treatments.
- increased risk of infection, as a result of low white blood cell count. The signs of infection include fever over 38°C (100°F), chills or sweating, sore throat or coughing, redness or swelling around a cut, wound or a catheter site, a burning feeling when you urinate, unusual vaginal itching or discharge.
- nausea and vomiting,
- fatigue, or feeling tired.
- mouth sores.
- Red coloration of your urine for 1 to 2 days after administration during active therapy

Rare side effects include:
- Severe adverse events such as local tissue damages due to leakage of DOXORUBICIN from your vein into surrounding tissues with intravenous injection might be observed.
- Damage to the heart muscle, which can cause symptoms such as shortness of breath, swelling in the ankles, and fluid retention. If you have these symptoms, call your doctor right away. There are medicines to treat this condition.

DOXORUBICIN can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Common	• anorexia	✓	
	• diarrhea		✓
	• infection		✓
	• hemorrhage		✓
	• irregular heartbeat, chest pain, swelling of the ankles, shortness of breath / cardiac problems		✓
	• pain at the site of the injection rash/itch/redness/ skin allergy		✓
Un-common	• loss of monthly periods		✓
	• allergy/anaphylaxis		✓
	• blood clot		✓
	• digestive inflammation, digestive tract bleeding (bloody stools, bloody vomit), color change of the oral mucosa		✓
	• dehydration		✓
	• hot flashes		✓
	• shock		✓
	• skin and nail changes , tingling sensation, urticaria		✓

This is not a complete list of side effects. For any unexpected effects while taking DOXORUBICIN, contact your doctor or pharmacist.

HOW TO STORE IT

DOXORUBICIN 2mg/mL shall be stored under refrigeration (2-8^{o}C), protected from light and retained in carton until time of use. Discard unused solution.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at: www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found at: http://www.pfizer.ca or by contacting the sponsor, Pfizer Canada Inc., at: 1-800-463-6001

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