

DOXORUBICIN**ADRIBLASTINA RD**

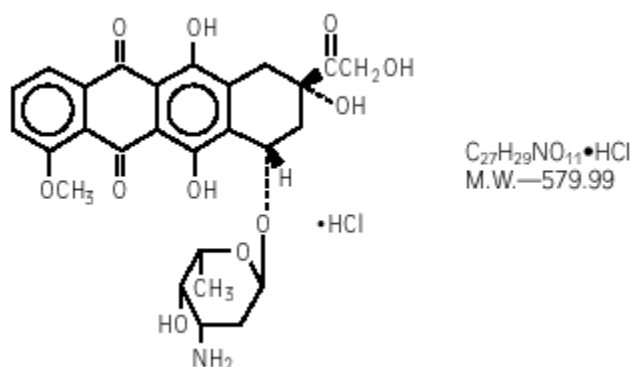
50 mg Lyophilized Powder for Injection (IV)

**1.0 PHARMACOLOGIC CATEGORY**

Antineoplastic (Anthracycline)

2.0 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- α -L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxylacetyl)-1-methoxy-, hydrochloride (8S-cis)-. The structural formula is as follows:



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 (Adriblastina RD) 50 mg Lyophilized Powder for Injection (IV) is provided as porous, red freeze-dried cake or mass. When reconstituted, doxorubicin (Adriblastina RD) 50 mg Lyophilized Powder for Injection (IV) appears as a clear and clean red solution.

3.0 FORMULATION/COMPOSITION**Doxorubicin (Adriblastina RD) 50 mg Lyophilized Powder for Injection (IV):**

Each vial contains 50 mg of doxorubicin hydrochloride.

4.0 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Doxorubicin is indicated in the treatment of the following cancers:

- acute lymphoblastic leukemia
- acute myelogenous leukemia
- chronic leukemias
- Hodgkin's & non-Hodgkin's lymphoma
- multiple myeloma
- osteosarcoma
- Ewing's sarcoma
- soft tissue sarcoma
- neuroblastoma
- rhabdomyosarcoma
- Wilms' tumor
- breast cancer, including as a component of adjuvant therapy in women with evidence of axillary lymph node involvement following resection of primary breast cancer
- endometrial cancer
- ovarian cancer
- non-seminomatous testicular cancer
- prostate cancer
- transitional cell bladder cancer
- lung cancer
- stomach (gastric) cancer
- primary hepatocellular cancer
- head and neck cancer
- thyroid cancer

4.2 Dosage and method of administration

Doxorubicin is usually administered by intravenous injection. Intravesical and intra-arterial routes may be used as indicated.

Intravenous (IV) Administration

The total doxorubicin 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.

Doxorubicin should be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or 5% glucose solution) for not less than 3 minutes and not more than 10 minutes to minimize the risk of thrombosis or perivenous extravasation. 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 Section **4.4 Special Warnings and Precautions for Use**).

Standard starting dose regimens

As a single agent, the recommended standard starting dose of doxorubicin per cycle in adults is 60-90 mg/m² of body surface area. The total starting dose per cycle may be given as a single dose or divided over 3 successive days or given on days 1 and 8. Under conditions of normal recovery from drug-induced toxicity (particularly bone marrow depression and stomatitis), each treatment cycle could be repeated every 3 to 4 weeks. Administration of doxorubicin in a weekly regimen of 10-20 mg/m² has also been shown to be effective. If doxorubicin is used in combination with other cytotoxic drugs with potentially overlapping toxicities, the recommended dose per cycle is in the 30-60 mg/m² range.

Adjuvant therapy

In a large randomized study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-15 of patients with early breast cancer involving axillary lymph nodes, (see Sections **4.8 Undesirable Effects** and **5.1 Pharmacodynamic Properties, Clinical Studies**) 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

Hepatic Dysfunction

Dose reductions are recommended in patients with the following serum chemistry values:

- Bilirubin 1.2 to 3 mg/dL: ½ of recommended starting dose.
- Bilirubin > 3 mg/dL: ¼ of recommended starting dose.

Doxorubicin should not be administered to patients with severe hepatic impairment (see Section **4.3 Contraindications**).

Other Special Populations

Lower starting doses or longer intervals between cycles may need to be considered for heavily pre-treated patients, children, elderly patients, obese patients, or patients with neoplastic bone marrow infiltration (see Section **4.4 Special Warnings and Precautions for Use**).

Intravesical Administration

Doxorubicin administered intravesically can be used for the treatment of superficial bladder tumors or as prophylaxis to reduce recurrence after transurethral resection. Intravesical administration is not suitable for the treatment of invasive tumors that have penetrated the muscular layer of the bladder wall. Instillations of 30-50 mg in 25-50 mL of saline solution are recommended. In the case of local toxicity (chemical cystitis), the dose should be instilled in 50-100 mL of saline solution. Patients may continue to receive

instillations in weekly to monthly intervals (see Section **4.4 Special Warnings and Precautions for Use**).

Doxorubicin should be instilled using a catheter and retained intravesically for 1 to 2 hours. 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 undue 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.

Intra-arterial Administration

Doxorubicin has been also used by the intra-arterial route in an attempt to produce intense local activity with reduced systemic toxicity in patients with hepatocellular carcinoma. Since this technique is potentially hazardous and can lead to widespread necrosis of the perfused tissue, intra-arterial administration should only be attempted by those physicians fully trained with this technique. Patients may receive an infusion into the main hepatic artery in doses of 30 to 150 mg/m² at intervals of 3 weeks to 3 months, with higher doses reserved for administration with concurrent extracorporeal drug elimination. Lower doses are suitable for administration of doxorubicin with iodized oil (see Section **4.4 Special Warnings and Precautions for Use**).

4.3 Contraindications

Hypersensitivity to doxorubicin or any other component of the product (e.g., methyl p-hydroxybenzoate 1 mg, lactose monohydrate 50 mg), other anthracyclines, or anthracenediones.

Intravenous (IV) use:

- persistent myelosuppression
- severe hepatic impairment
- severe myocardial insufficiency
- recent myocardial infarction
- severe arrhythmias
- previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones (see Section **4.4 Special Warnings and Precautions for Use**).

Intravesical use:

- urinary infections
- inflammation of the bladder
- hematuria

4.4 Special warnings and precautions for use

General

Doxorubicin should be administered only under the supervision of physicians experienced in the use of cytotoxic therapy.

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

The systemic clearance of doxorubicin is reduced in obese patients (i.e., >130% ideal body weight) (see Section **4.2 Dosage and Method of Administration, Other Special Populations**).

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 electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for 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 have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

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. The technique used for assessment should be consistent throughout follow-up.

The probability of developing CHF, estimated around 1% to 2% at a cumulative dose of 300 mg/m², slowly increases up to the total cumulative dose of 450-550 mg/m². Thereafter, the risk of developing CHF increases steeply, and it is recommended not to exceed a maximum cumulative dose of 550 mg/m².

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 (e.g., trastuzumab). Anthracyclines including doxorubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see Section **4.5 Interactions with other medicinal products and other forms of interaction**). 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 variable, Trastuzumab may persist in the circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months 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. However, cardiotoxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.

Children and adolescents are at an increased risk for developing delayed cardiotoxicity following doxorubicin administration. Females may be at greater risk than males. Follow-up cardiac evaluations are recommended periodically to monitor for this effect.

It is probable that the toxicity of doxorubicin and other anthracyclines or anthracenediones is additive.

Hematologic Toxicity

As with other cytotoxic agents, doxorubicin may produce 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.

Secondary Leukemia

Secondary leukemia, with or without a pre-leukemic phase, has been reported in patients treated with anthracyclines (including doxorubicin). 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 pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukemias can have a 1- to 3-year latency period.

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.

Hepatic Function

The major route of elimination of doxorubicin is the hepatobiliary system. Serum total bilirubin should be evaluated before and during treatment with doxorubicin. Patients with elevated bilirubin may experience slower clearance of drug with an increase in overall toxicity. Lower doses are recommended in these patients (see Section **4.2 Dosage and Method of Administration, *Hepatic Dysfunction***). Patients with severe hepatic impairment should not receive doxorubicin (see Section **4.3 Contraindications**).

Effects at Site of Injection

Phleboscrosis 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 Section **4.2 Dosage and Method of Administration**).

Extravasation

Extravasation of doxorubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis), and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of doxorubicin, the drug infusion should be immediately stopped.

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.

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.

Other

Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhanced hepatotoxicity of 6-mercaptopurine have been reported. Radiation-induced toxicities (myocardium, mucosae, skin and liver) have also been reported.

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.

Additional Warnings and Precautions for Other Routes of Administration

Intravesical Route

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).

Intra-arterial Route

Intra-arterial administration of doxorubicin (transcatheter arterial embolization) may be employed for the localized or regional therapy of primary hepatocellular carcinoma or liver metastases. Intra-arterial administration may produce (in addition to systemic toxicity qualitatively similar to that observed following intravenous administration of doxorubicin) gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to drug-induced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue.

Embryo-fetal Toxicity

Doxorubicin can cause genotoxicity. An effective method of contraception is required for both male and female patients during and for a period after treatment with doxorubicin. Patients desiring to have children after completion of therapy should be advised to obtain genetic counseling if appropriate and available.

(see Sections **4.6 Fertility, Pregnancy and Lactation** and **5.3 Preclinical Safety Data**).

4.5 Interactions with other medicinal products and other forms of interaction

Doxorubicin is a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (e.g., verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (e.g., phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin.

The addition of cyclosporine to doxorubicin may result in increases in area under the concentration-time curve (AUC) for both doxorubicin and doxorubicinol, 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 have also been described with concomitant administration of cyclosporine and doxorubicin.

Doxorubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/hematologic and gastrointestinal effects (see Section **4.4 Special Warnings and Precautions for Use**). 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.

Paclitaxel can cause increased plasma-concentrations of doxorubicin and/or its metabolites when given prior to doxorubicin. Certain data indicate that this effect is minor when anthracycline is administered prior to paclitaxel.

Both increases (21% - 47%) and no change in the AUC of doxorubicin were observed with concomitant treatment with sorafenib 400 mg twice daily. The clinical significance of these findings is unknown.

4.6 Fertility, pregnancy and lactation

(See also Section **5.3 Preclinical Safety Data**).

Impairment of Fertility

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.

In men, 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. Both men and women should seek advice on fertility preservation before treatment.

Pregnancy

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 apprised of the potential hazard to the fetus.

Women of Childbearing Potential/Contraception in Males and Females

Women of childbearing potential should be advised to avoid becoming pregnant during treatment and to use effective contraceptive methods during treatment and for at least 6 months and 10 days after last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with doxorubicin and for at least 3 months and 10 days after last dose.

Lactation

Doxorubicin is excreted in breast milk (see Section **5.2 Pharmacokinetic Properties**). Because of the potential for serious reactions in nursing infants from doxorubicin women should not breastfeed while undergoing treatment with doxorubicin and for at least 10 days after last dose.

4.7 Effects on ability to drive and use machines

The effect of doxorubicin on the ability to drive or use machinery has not been systematically evaluated.

4.8 Undesirable effects

Adverse reactions reported in association with doxorubicin therapy are listed below by MedDRA System Organ Class and by frequency. Frequencies are defined as: Very common ($\geq 10\%$), Common ($\geq 1\%$, $< 10\%$), Uncommon ($\geq 0.1\%$, $< 1\%$), Rare ($\geq 0.01\%$, $< 0.1\%$), Very rare ($< 0.01\%$), and Not known (cannot be estimated from available data).

Adverse Reactions Table

Infections and Infestations	
Very common	Infection
Common	Sepsis
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	
Not known	Acute lymphocytic leukemia, Acute myeloid leukemia
Blood and Lymphatic System Disorders	
Very common	Leukopenia, Neutropenia, Anemia, Thrombocytopenia
Immune System Disorders	
Not known	Anaphylactic reaction
Metabolism and Nutrition Disorders	
Very common	Decreased appetite
Not known	Dehydration, Hyperuricemia
Eye Disorders	
Common	Conjunctivitis
Not known	Keratitis, Lacrimation increased
Cardiac Disorders	
Common	Cardiac failure congestive, Sinus tachycardia
Not known	Atrioventricular block, Tachyarrhythmia, Bundle branch block
Vascular Disorders	
Uncommon	Embolism
Not known	Shock, Hemorrhage, Thrombophlebitis, Phlebitis, Hot flush
Gastrointestinal Disorders	
Very common	Mucosal inflammation/Stomatitis, Diarrhea, Vomiting, Nausea
Common	Esophagitis, Abdominal pain
Not known	Gastrointestinal hemorrhage, Gastritis erosive, Colitis, Mucosal discoloration
Skin and Subcutaneous Tissue Disorders	
Very common	Palmar-plantar erythrodysesthesia syndrome, Alopecia
Common	Urticaria, Rash, Skin hyperpigmentation, Nail hyperpigmentation
Not known	Photosensitivity reaction, Recall phenomenon, Pruritus, Skin disorder
Renal and Urinary Disorders	
Not known	Chromaturia ^a
Reproductive System and Breast Disorders	
Not known	Amenorrhea, Azoospermia, Oligospermia
General Disorders and Administration Site Conditions	
Very common	Pyrexia, Asthenia, Chills
Common	Infusion site reaction
Not known	Malaise

Investigations	
Very common	Ejection fraction decreased, Electrocardiogram abnormal, Transaminases abnormal, Weight increased ^b
^a For one to two days after administration. ^b Reported in patients with early breast cancer receiving doxorubicin-containing adjuvant therapy (NSABP B-15 trial).	

4.9 Overdose

Acute overdosage with doxorubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac alterations.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*.

The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. 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.

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 1998 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 analyses. The principal endpoints for the adjuvant chemotherapy trials were disease-free survival (DFS) and overall survival (OS). The meta-analyses allowed comparisons of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) to no chemotherapy (19 trials including 7523 patients) and comparisons of doxorubicin-containing regimens with CMF as an active control (6 trials including 3510 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 0.71-0.82) and for OS was 0.86 (95% CI 0.80-0.93). Based on a conservative estimate of CMF effect (lower 2-sided 95% confidence limit of hazard ratio) and 75% retention of CMF effect on DFS, it was determined that the doxorubicin containing-regimens would be considered as non-inferior to CMF if the upper 2-sided 95% confidence limit of the hazard ratio was less than 1.06, i.e., not more than 6% worse than CMF. A similar calculation for OS would require a non-inferiority margin of 1.02.

Six randomized trials in the EBCTCG meta-analysis compared doxorubicin-containing regimens to CMF. A total of 3510 women with early breast cancer involving axillary lymph nodes were evaluated; approximately 70% were pre-menopausal and 30% were post-menopausal. 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 0.82-1.01) and for OS was 0.91 (95% CI 0.81-1.03).

The largest of the 6 studies in the EBCTCG meta-analysis, a randomized, open-label, multicenter trial (NSABP B-15) was conducted in approximately 2300 women (80% pre-menopausal; 20% post-menopausal) with early breast cancer involving axillary lymph nodes. In this trial, 6 cycles of conventional CMF was compared to 4 cycles of doxorubicin and cyclophosphamide (AC) and 4 cycles of AC followed by 3 cycles of CMF. No statistically significant differences in terms of DFS or OS were observed.

5.2 Pharmacokinetic properties

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% to 76% and is independent of plasma concentration of doxorubicin up to 1.1 µg/mL.

Doxorubicin was excreted in the milk of one lactating patient, with peak milk concentration 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 intravenous infusion. The peak concentration of doxorubicinol in milk at 24 hours was 0.11 µg/mL and AUC up to 24 hours was 9.0 µg·h/mL while the AUC for doxorubicin was 5.4 µg·h/mL.

Doxorubicin does not cross the blood brain barrier.

Metabolism

Enzymatic reduction at the 7 position and cleavage of the daunosamine sugar yields aglycones which are accompanied by free radical formation, the local production of which may contribute to the cardiotoxic activity of doxorubicin. Disposition of doxorubicinol (DOX-OL) in patients is formation rate limited, with the terminal half-life of DOX-OL being similar to doxorubicin. The relative exposure of DOX-OL, i.e., the ratio between the AUC of DOX-OL and the AUC of doxorubicin, compared to doxorubicin ranges between 0.4 and 0.6.

Excretion

Plasma clearance is in the range 324 to 809 mL/min/m² and is predominantly 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 time period. In urine, <3% of the dose was recovered as DOX-OL over 7 days.

Systemic clearance of doxorubicin is significantly reduced in obese women with ideal body weight greater than 130%. There was a significant reduction in clearance without any change in volume of distribution in obese patients when compared with normal patients with less than 115% ideal body weight (see Section **4.2 Dosage and Method of Administration, *Other Special Populations***).

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 in 52 children greater than 2 years of age (1540 mL/min/m²) was increased compared with adults. However, clearance in infants younger than 2 years of age (813 mL/min/m²) was decreased compared with older children and approached the range of clearance values determined in adults (see Sections **4.2 Dosage and Method of Administration** and Section **4.4 Special Warnings and Precautions for Use**).

Geriatric

While the pharmacokinetics of elderly subjects (≥65 years of age) have been evaluated, no dosage adjustment is recommended based on age.

Gender

A published clinical study involving 6 men and 21 women with no prior anthracycline therapy reported a significantly higher median doxorubicin clearance in the men compared to the women (1088 mL/min/m² versus 433 mL/min/m²). However, the terminal 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 Section **4.2 Dosage and Method of Administration, Hepatic Dysfunction**).

Renal Impairment

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

5.3 Preclinical safety data

Carcinogenesis & Mutagenesis

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.

Impairment of Fertility

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

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

See outer package for the expiry date of the product.

6.2 Storage Condition (s)

50 mg Lyophilized Powder for Injection (IV): Store at temperatures not exceeding 30°C.

6.3 Availability

50 mg vial containing 50 mg of doxorubicin hydrochloride as freeze-dried powder in a colorless glass vial.

6.4 Incompatibilities

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.

Doxorubicin should not be mixed with fluorouracil (e.g., 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.

6.5 Special precautions for disposal and other handling

Preparation of the freeze-dried powder for intravenous administration

Dissolve powder in sodium chloride/water for injection. The vial contents are under negative pressure. To minimize aerosol formation during reconstitution; particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided.

Protective measures

The following protective recommendations are given due to the toxic nature of this substance:

- Personnel should be trained in good techniques for reconstitution and handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling doxorubicin should wear protective clothing: goggles, gowns 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 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.

7.0 FDA REGISTRATION NUMBER

50 mg Lyophilized Powder for Injection (IV): DRP-3413

8.0 DATE OF FIRST AUTHORIZATION

50 mg Lyophilized Powder for Injection (IV): 03 Jan 1992

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:

Latina Pharma S.p.A.
Via Murillo, 7,
Sermoneta (LT), 04013, Italy

Marketing Authorization Holder:

Pfizer, Inc.
19F – 20F, 8 Rockwell Building, Hidalgo Drive,
Rockwell Center, Poblacion, Makati City 1210,
Metro Manila, Philippines

Revision No.: 10.3
Revision Date: 26 March 2024
Reference No.: CDS version 10.0 and
11.0/Manufacturer and MAH address update
+ BOH mandated changes/Manufacturer
name change
Reference Date: 21 Nov 2018 and 10 Sep
2021