פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

Prescribing information

ADRIBLASTINA PFS

Vials

WARNING

1. Severe local tissue necrosis will occur if there is extravasation during administration (See Dosage and Administration). Doxorubicin must not be given by the intramuscular, subcutaneous or intrathecal route.
2. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure (CHF) may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m^2 of doxorubicin, 3 to 5% at a dose of 400 mg/m^2, 5 to 8% at 450 mg/m^2 and 6 to 20% at 500 mg/m^2. The risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 450 mg/m^2. This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy or with pre-existing heart disease. Risk of cardiotoxicity also increases with previous or concomitant therapy with other anthracyclines or anthracenediones (such as daunorubicin, idarubicin and mitoxantrone), and drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g. trastuzumab). Anthracycline-based therapy should be avoided for up to 24 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.
3. Dosage should be reduced in patients with impaired hepatic function.
4. Severe myelosuppression may occur.
5. Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.
6. 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
7. Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) has been reported in patients treated with anthracyclines, including doxorubicin (see ADVERSE REACTIONS).

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*)-.

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.

Adriblastina PFS (Doxorubicin Hydrochloride Injection, USP) is a sterile parenteral, isotonic solution for intravenous use only, containing no preservative, available in 5 mL (10 mg) and 25 mL (50 mg) vials.
Each mL contains doxorubicin HCl 2 mg, USP and the following inactive ingredients: sodium chloride 0.9% and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target pH of 3.0.

Clinical pharmacology

The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. 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 cytocidal activity. Doxorubicin cellular membrane binding may effect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generate highly reactive species including the hydroxyl free radical OH*. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level.
Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy to testes in rats and dogs.

Pharmacokinetics

Pharmacokinetic studies, determined in patients with various types of tumors undergoing either single or multi-agent therapy have shown that doxorubicin follows a multiphasic disposition after intravenous injection. The initial distributive half-life of approximately 5.0 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 volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. Approximately 40% of the 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. 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 μM. Enzymatic reduction at the 7 position and cleavage of the daunosamine sugar yields aglycones which are accompanied by free radical formation, the local production of which may contribute to the cardiotoxic activity of doxorubicin. Disposition of doxorubicinol (DOX-OL) in patients is formation rate limited. The terminal half-life of DOX-OL is similar to doxorubicin. The relative exposure of DOX-OL, , i.e., the ratio between the AUC of DOX-OL and the AUC of doxorubicin, compared to doxorubicin ranges between 0.4 to 0.6. In urine, <3% of the dose was recovered as DOX-OL over 7 days.
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.
In four patients, dose-independent pharmacokinetics have been shown for doxorubicin in the dose range of 30 to 70 mg/m^2. Systemic clearance of doxorubicin is significantly reduced in obese women with ideal body weight greater than 130%. There was a significant reduction in clearance without any change in volume of distribution in obese patients when compared with normal patients with less than 115% ideal body weight. The clearance of doxorubicin and doxorubicinol was also reduced in patients with impaired hepatic function. Doxorubicin was excreted in the milk of one lactating patient, with peak milk concentration at 24 hours after treatment being approximately 4.4 -fold greater than the Corresponding Plasma Concentration. Doxorubicin was detectable in the milk up to 72 hours after therapy with 70 mg/m^2 of doxorubicin given as a 15 minute intravenous infusion and 100 mg/m^2 of cisplatin as a 26 hour intravenous infusion. The peak concentration of doxorubicinol in milk at 24 hours was 0.11 μM and AUC up to 24 hours was 9.0 μM. hr while the AUC for doxorubicin was 5.4 μM. hr.
Doxorubicin does not cross the blood brain barrier.

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 Section Dosage and administration and Section 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 Dosage and administration).
Renal Impairment. The influence of renal function on the pharmacokinetics of doxorubicin has not been evaluated.

Indications

Adriblastina PFS has been used successfully to produce regression in a variety of neoplastic conditions, such as carcinoma of the breast, lung, bladder, thyroid, and also ovarian carcinomas, bone and soft-tissue sarcomas, Hodgkin's and non-Hodgkin's lymphomas, neuroblastomas, Wilms' tumour, acute lymphoblastic leukaemia and acute myeloblastic leukaemia.

Contraindications
Hypersensitivity to doxorubicin or any other component of the product, 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, 24 weeks after stopping treatment with trastuzumab. (see Section **Special warnings and precautions for use)**

Intravesical use:
- Urinary infections
- Inflammation of the bladder
- Hematuria

Special warnings and precautions for use

General
Doxorubicin is not an anti-microbial agent.

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).

Cardiac function. Special attention must be given to the cardiotoxicity induced by doxorubicin. Irreversible myocardial toxicity, manifested in its most severe form by life threatening and potentially fatal congestive heart failure, may occur either during therapy or months to years after termination of therapy. *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.

The probability of developing impaired myocardial function, based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m^2 of doxorubicin, 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 given in a schedule of a bolus injection once every 3 weeks. In a retrospective review by Von Hoff et al, the probability of developing congestive heart failure was reported to be 5/168 (3%) at a cumulative dose of 430 mg/m^2 of doxorubicin, 8/110 (7%) at 575 mg/m^2 and 3/14 (21%) at 728 mg/m^2. The cumulative incidence of CHF was 2.2%. In a prospective study of doxorubicin in combination with cyclophosphamide, fluorouracil and/or vincristine in patients with breast cancer or small cell lung cancer, the cumulative incidence of congestive heart failure was 5 to 6%. The probability of CHF at various cumulative doses of doxorubicin was 1.5% at 300 mg/m^2, 4.9% at 400 mg/m^2, 7.7% at 450 mg/m^2 and 20.5% at 500 mg/m^2.
Cardiotoxicity may occur at lower doses in patients with prior mediastinal/pericardial irradiation, concurrent cyclophosphamide therapy and advanced age. Data also suggest that pre-existing, active or dormant heart disease is a co-factor for increased risk of doxorubicin cardiotoxicity. In such cases, cardiac toxicity may occur at doses lower than the respective recommended cumulative dose of doxorubicin. Studies have suggested that concomitant administration of doxorubicin and calcium channel entry blockers may increase the risk of doxorubicin cardiotoxicity. The total dose of doxorubicin administered to the individual patient should also take into account previous or concomitant therapy with other anthracyclines or anthracenediones (such as daunorubicin, idarubicin and mitoxantrone), and concomitant use of drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g. trastuzumab). Anthracyclines 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 half-life of trastuzumab is approximately 28.5 days and may persist in the circulation for up to 24 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 24 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended**.** Cardiomyopathy and/or congestive heart failure may be encountered several months or years after discontinuation of doxorubicin therapy.

The risk of congestive heart failure and other acute manifestations of doxorubicin cardiotoxicity in children may be as much or lower than in adults. Children appear to be at particular risk for developing delayed cardiac toxicity in that doxorubicin induced cardiomyopathy impairs myocardial growth as children mature, subsequently leading to possible development of congestive heart failure during early adulthood. As many as 40% of children may have subclinical cardiac dysfunction and 5 to 10% of children may develop congestive heart failure on long term follow-up. This late cardiac toxicity may be related to the dose of doxorubicin. The longer the length of follow-up the greater the increase in the detection rate.
Treatment of doxorubicin induced congestive heart failure includes the use of digitalis, diuretics, after load reducers such as angiotensin I converting enzyme (ACE) inhibitors, low

salt diet, and bed rest. Such intervention may relieve symptoms and improve the functional status of the patient.

Monitoring Cardiac Function

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. In adult patients severe cardiac toxicity may occur precipitously without antecedent ECG changes. Cardiomyopathy induced by anthracyclines is usually associated with very characteristic histopathologic changes on an endomyocardial biopsy (EM biopsy), and a decrease of left ventricular ejection fraction (LVEF), as measured by multi-gated radionuclide angiography (MUGA scans) and/or echocardiogram (ECHO), from pretreatment baseline values. However, it has not been demonstrated that monitoring of the ejection fraction will predict when individual patients are approaching their maximally tolerated cumulative dose of doxorubicin. A baseline cardiac evaluation with an ECG, LVEF, and/or an echocardiogram (ECHO) is recommended especially in patients with risk factors for increased cardiac toxicity (pre existing heart disease, mediastinal irradiation, or concurrent cyclophosphamide therapy). Repeated MUGA or ECHO determinations of LVEF should be obtained at a cumulative dose of doxorubicin particularly with higher, cumulative anthracycline doses (of at least 400 mg/m^2) and periodically thereafter during the course of therapy. 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/m^2, slowly increases up to the total cumulative dose of 450-550 mg/m^2. Thereafter, the risk of developing CHF increases steeply, and it is recommended not to exceed a maximum cumulative dose of 550 mg/m^2.

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.

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

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. In adults, a 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of 45%, or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function. In children, deterioration in cardiac function during or after the completion of therapy with doxorubicin is indicated by a drop in fractional shortening (FS) by an absolute value of 10 percentile units or below 29%, and a decline in LVEF of 10 percentile units or an LVEF below 55%. In general, if test results indicate deterioration in cardiac function associated with doxorubicin, the benefit of continued therapy should be carefully evaluated against the risk of producing irreversible cardiac damage.
Acute life-threatening arrhythmias have been reported to occur during or within a few hours after doxorubicin administration.
Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported. Radiation induced toxicity to the myocardium, mucosae, skin and liver have been reported to be increased by the administration of doxorubicin.

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.
White blood counts as low as 1000/mm^3 are to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or suspension or delay of doxorubicin therapy. Persistent severe myelosuppression may result in superinfection or hemorrhage.

Secondary Leukemia. Secondary leukemia, with or without a preleukemic 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 pretreated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukemias can have a 1- to 3-year latency period.

Hepatic Function. Since metabolism and excretion of doxorubicin occurs predominantly by the hepatobiliary route, toxicity to recommended doses of doxorubicin can be enhanced by hepatic impairment; therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin. 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 **Dosage and administration**). Patients with severe hepatic impairment should not receive doxorubicin (see **Contraindications).**

Gastrointestinal. Doxorubicin is emetigenic. 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 i.v. push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

Effects at Site of Injection. 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 Section **Dosage and administration).**

Extravasation On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation, local pain, severe tissue lesions (vesication, severe cellulitis), and necrosis, even if blood returns well on aspiration of the infusion needle (See Section **Dosage and administration**). If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein.

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.

Pregnancy*:* Category D-Safe use of doxorubicin in pregnancy has not been established. Doxorubicin is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. There are no adequate and well-controlled studies in pregnant women. Doxorubicin has been implicated in causing fetal harm when administered to a pregnant woman. If doxorubicin is to be used during pregnancy, or if the patient becomes pregnant during therapy,

the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.
***Nursing mothers*:** Doxorubicin is excreted in breast milk. Women should not breastfeed while undergoing treatment with doxorubicin

Other: Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported. Radiation induced toxicity to the myocardium, mucosae, skin and liver have been reported.
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.

Information for patients

Adriblastina PFS imparts a red coloration to the urine for 1 to 2 days after administration, and patients should be advised to expect this during active therapy.

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.

Carcinogenesis, mutagenesis

Formal long-term carcinogenicity studies have not been conducted with doxorubicin. Doxorubicin and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models (including bacterial systems, mammalian cells in culture, and female Sprague Dawley rats).

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.

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.

A variant of chemotherapy-related acute non-lymphocytic leukemia has been reported to occur infrequently a few years after multiple drug treatment of some neoplasms, which sometimes included doxorubicin. The exact role of doxorubicin has not been elucidated.

Drug interactions

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 (eg, verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (eg, 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 cyclosporin 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 **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 administrated 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

Literature contain the following drug interactions with doxorubicin in humans: streptozocin (Zanosar) may inhibit the hepatic metabolism, and administration of live vaccines to immunosuppressed patients, including those undergoing cytotoxic chemotherapy, may be hazardous. Information on other potential drug interactions may be found in the literature.

Laboratory tests

Initial treatment with doxorubicin requires observation of the patient and periodic monitoring of complete blood counts, hepatic function tests, and radionuclide left ventricular ejection fraction (See Special warnings and precaution section).

Adverse reactions

Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity. Other reactions reported are:

Infections and infestations: infection, sepsis/septicemia

Neoplasms benign and malignant: acute lymphocytic leukemia, acute myelogenous leukemia

Blood and lymphatic system disorders: leukopenia, neutropenia, anemia, thrombocytopenia

Immune system disorders: anaphylaxis

Metabolism and nutrition disorders: anorexia, dehydration, hyperuricemia

Eye disorders: conjunctivitis/keratitis, lacrimation

Cardiac disorders: cardiotoxicity (see warnings), sinus tachycardia, tachyarrhythmias, atrioventricular and bundle branch block, congestive heart failure

Vascular disorders: hemorrhage, hot flashes, phlebitis, thrombophlebitis, phlebosclerosis, thromboembolism, shock

Gastrointestinal disorders: nausea/vomiting, mucositis/stomatitis, hyperpigmentation of oral mucosa, esophagitis, abdominal pain, gastric erosions, gastrointestinal tract bleeding, ulceration and necrosis of colon, diarrhea, colitis

Skin and subcutaneous tissue disorders: alopecia, local toxicity, rash/itch, skin changes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin ('radiation recall reaction'), urticaria, acral erythema, palmar plantar erythrodysaesthesia.

Renal and urinary disorders: *red coloration of urine for 1 to 2 days after administration*

Reproductive system and breast disorders: amenorrhea, oligospermia, azoospermia

General disorders and administration site conditions: malaise/asthenia, fever, chills. A case of apparent cross sensitivity to lincomycin has been reported.

Investigations: ECG abnormalities, asymptomatic reductions in left ventricular ejection fraction, changes in transaminase levels

Local: Severe cellulitis, vesication and tissue necrosis will occur if extravasation of doxorubicin occurs during administration. Erythematous streaking along the vein proximal to the site of injection had been reported (See Dosage and administration).

Adverse Reactions in Patients with Early Breast Cancer Receiving Doxorubicin-Containing Adjuvant Therapy: Safety data were collected from approximately 2300 women who participated in a randomized, open-label trial (NSABP B-15) evaluating the use of AC versus CMF in the treatment of early breast cancer involving axillary lymph nodes. The most relevant adverse events reported in this study were consistent with the safety adverse event profile for doxorubicin. Additional adverse events include:

Investigations: weight gain.

Overdosage

Acute overdosage with doxorubicin enhances the toxic effect of mucositis, leukopenia and thrombocytopenia and acute cardiac alterations. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antimicrobials, platelet transfusions and symptomatic treatment of mucositis. Use of hemopoietic growth factor (G-CSF, GM-CSF) may be considered.
Cumulative dosage with doxorubicin increases the risk of cardiomyopathy and resultant congestive heart failure (See Specail warnings and precautions section). Treatment consists of vigorous management of congestive heart failure with digitalis preparations, diuretics, and after-load reducers such as ACE inhibitors.

Dosage and administration

Adriblastina PFS is not active orally, and must not be administered intramuscularly or intrathecally. Adriblastina PFS should be administered solely by intravenous injection or - in the case of local-regional treatment of tumours - by slow intra-arterial infusion.

Care in the administration of Adriblastina PFS will reduce the chance of perivenous infiltration (See Special warnings and precautions). It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 min. q.i.d. X 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.

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.

Intravenous route: When Adriblastina PFS is used as a single antitumour agent the recommended dose in adults is 60-90 mg/m^2 of body surface area by intravenous injection every three weeks dependent on bone-marrow reserves. The lower dose (60 mg/m^2) is recommended for patients with inadequate marrow reserves as a result of old age, previous therapy or neoplastic marrow infiltration. Lower starting doses or longer intervals between cycles may need to be considered also for heavily pretreated patients, children, elderly patients, obese patients, or patients with neoplastic bone marrow infiltration
The above dose can be given as a single injection or subdivided over 3 consecutive days or given on days 1 and 8. An alternative dosage of 30 mg/m^2/day i.v. for three consecutive days has been suggested specifically for paediatric use: the course should be repeated every 4 weeks.
The cumulative dose of Adriblastina PFS by the intravenous route, irrespective of the dosage schedule, should not exceed 550 mg/m^2 of body surface area (see section Special Warnings and precautions).
Adriblastina PFS is presently also used extensively in combination chemotherapy at usual doses of 30-60 mg/m^2 every 3-4 weeks if combined with other myelosuppressive drugs and at doses of 60-90 mg/m^2 if used in combination with drugs that are not myelosuppressive.
The dosage of Adriblastina PFS should be reduced in patients with impaired hepatic function, to prevent an increase of overall toxicity.
Generally, when serum bilirubin levels are approximately 1.2-3 mg% and BSP retention is 9-15%, it is recommended that half the normal dose of Adriblastina PFS be used. If serum bilirubin levels and BSP retention are even higher, it is recommended that a quarter of the usual dose be given. In view of the low renal excretion of Adriblastina PFS, moderate impairment of renal function does not usually require a reduction in the recommended dose.

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, the combination dosage regimen of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) was administered intravenously on day 1 of each 21-day treatment cycle. Four cycles of treatment were administered .

Intravesical Administration Doxorubicin administered intravesically can be used for the treatment of superficial bladder tumors or as prophylaxis to reduce recurrence after trans-urethral 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 **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 to150 mg/m^2 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 **Special Warnings and Precautions for Use**).

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 **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 Section **Special Warnings and Precautions for Use**).

It is recommended that Adriblastina PFS be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein, and the dosage. However, the dose should be administered in not less than 3 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 warnings). Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

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 premenopausal and 30% were postmenopausal. At the time of the meta-analysis, 1745 first recurrences and 1348 deaths had occurred. Analyses demonstrated that doxorubicin-containing regimens retained at least 75% of the historical CMF adjuvant effect on DFS and are effective. The hazard ratio for DFS (dox: CMF) was 0.91 (95% CI 0.82-1.01) 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% premenopausal; 20% postmenopausal) 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.

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 (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.

Special Precautions for Storage
Storage of the solution for injection at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after two to a maximum of four hours equilibration at controlled room temperature (15 - 25ºC)**.**

Handling and disposal:
Skin reactions associated with doxorubicin have been reported. Skin accidentally exposed to doxorubicin should be rinsed copiously with soap and warm water, and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.
Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all the procedures recommended in the guidelines are necessary or appropriate.

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

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

List of Excipients

Hydrochloric acid
Sodium chloride
Water for Injection

How supplied:
Adriblastina PFS (Doxorubicin Hydrochloride Injection, USP)
Single dose vials:
Sterile single use only, contains no preservative.
10 mg vial, 2 mg/mL, 5 mL, single vial packs
50 mg vial, 2 mg/mL, 25 mL, single vial packs
Store under refrigeration, 2° to 8° C. Protect from light. Retain in carton until time of use.
Discard unused portion.

Manufacturers:
Actavis Italy SPA, Nerviano (Milano)

License Holder

Pfizer Pharmaceuticals Ltd., 9 Shenkar St. Herzliya Pituach 46725