ADRIBLASTINA®
(Doxorubicin hydrochloride)

1. NAME OF THE MEDICINAL PRODUCT

ADRIBLASTINA®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxorubicin hydrochloride 10 mg or 50 mg.

For a full list of excipients, see section **6.1. List of Excipients**.

3. PHARMACEUTICAL FORM

Powder for solution for injection

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Breast cancer. Osteogenic sarcoma and Ewing's sarcoma. Soft tissue sarcoma. Small cell anaplastic lung carcinoma. Malign lymphoma of both the types Hodgkin's disease and non-Hodgkin's disease. Urogenital and gynecological tumors like bladder cancer, cancer of the testis and uteral cancer. Paediatric solid tumors such as rhabdomyosarcoma, neuroblastoma, Wilm's tumour. Acute leukemias. To be attempted in: Carcinoma of the prostate. Carcinoma of the thryoid gland. Ovarial cancer, cervical cancer, vaginal cancer, head and neck cancer, ventricular cancer.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Posology

60-75 mg/m^2 as a single dose i.v. at intervals of 21 days. The lowest dose should be given to patients with myelosuppression. Alternatively 30 mg/m^2/day for 3 days at intervals of 4 weeks, or in breast cancer: 20 mg per week i.v. over 3 – 4 minutes each week, especially in palliative treatment of patients who do not tolerate the conventional treatment every 3 weeks.

Dose reduction: When the substance is given in combination with other cytostatic agents, the dose should be reduced to 30-60 mg/m^2. Further dose reduction should be done if the patient previously has received radiation treatment towards the mediastinum or if other anthracyclines have been administered previously. Prior to initiation of the treatment, a control of the liver function is recommended, based on conventional tests such as ASAT, ALAT, ALP and bilirubin. By impaired liver function the dose should be reduced according to the table below:

Serum bilirubin	Recommended dose
24-50 micromol/l	1/2 of the normal dose
>50 micromol/l	1/4 of the normal dose

In order to avoid cardiomyopathies a total dose of 550 mg/m^2 shall not be exceeded.

Method of administration
The substance should be administered as an intravenous injection by continuous drip with sodium chloride solution for infusion 9 mg/ml or glucose solution for infusion 50 mg/ml. The solution should be injected within 2 – 5 minutes.

In order to ensure the possibility of administering intravenous cytostatic treatment for a longer period of time, an arteriovenous shunt may be installed prior to initiation of the treatment.

Intravesical instillation has been attempted in connection with cancer of the bladder, see specialist literature.

4.3. CONTRAINDICATIONS

Hypersensitivity to the active substance, other anthracyclines or to any of the excipients listed in section 6.1. Pronounced myelosuppression induced by previous treatment with other cytostatic agents or by radiation treatment. Severe impairment of the liver. Previous treatment with anthracyclines up to their maximum cumulative dose (see section **4.2 Posology and Method of administration**).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Caution should be exercised in patients with cardiac disease in their medical history, and in patients who previously have been treated with anthracyclines or have received radiation treatment towards the mediastinum. Previous cardiac disease increases the risk of developing chronic cardiomyopathy. Left ventricle function should be monitored by LVEF measurement by ultrasound or cardiac scintigraphy in order to check the heart condition of the patient.

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/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.

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 Interaction 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.

Doxorubicin may potentiate the toxicity of other cytotoxic drugs, and adjustment of the dose may be required (see section **4.2 Posology and Method of administration**). Exacerbation of cyclophosphamide induced hemorrhagic cystitis and aggravated liver toxicity from 6-mercapturin have been reported. Radiation induced toxicity (the myocard, mucosa, skin and liver) has also been reported.

The systemic clearance of doxorubicin may be reduced in obese patients, and these should be monitored carefully during full dose treatment.

Extravasal injection

In order to reduce the risk of extravasal injections resulting in tissue damage, doxorubicin should be administered during continuous fluid infusion.

Avoid applying the drip at the back of the hand, close to joints, tendons or large blood vessels and nerves, as damage due to extravasal application of the cytostatics usually are more difficult to handle at such sites.

Doxorubicin is strongly toxic to tissues and may cause necroses which are very difficult to treat and which have a high risk of infections. If the patient indicates more than slight pain at the site of the injection, the injection should be discontinued. Alleviation of the patient's ailments has been attempted by cooling down the area and keeping it cooled down for 24 hours. Acute excision of the area infiltrated by doxorubicin should be considered – a surgeon should immediately be contacted to make a joint evaluation of any surgical measures. The patient should be monitored closely after the administration, as necroses may occur several weeks later. Necrotic wounds should be excised.

Doxorubicin is strongly toxic to tissues and may cause injuries to unprotected skin. If doxorubicin gets into direct contact with the skin or mucosa, the exposed area should be washed carefully with soap and water.

If the solution enters the eyes - rinse thoroughly with water or sterile saline solution. Then a physician should be contacted. If the irritation has not passed in 30 minutes an ophthalmologist should make further examinations.

The patient should be informed that the urine may take on a red colour.

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 counselling if appropriate and available (see sections **4.6 Fertility, pregnancy and lactation** and **5.3 Preclinical safety data**).

4.5. INTERACTION 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 cyclosporin and doxorubicin.

Doxorubicin is mainly used in combination with other cytotoxic drugs. 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 (see section **4.4. Special warnings and precautions for use**).
The combination of doxorubicin and cytarabine has in some cases caused bleedings, ulcerations and necrosis in mucosa of the colon in patients with acute myelogenous leukaemia.

4.6. FERTILITY, PREGNANCY AND LACTATION

Fertility

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

Men: Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa.

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

Pregnancy

Doxorubicin crosses the placenta and the substance has been demonstrated in phoetal tissue (in highest concentrations in liver, kidneys and lung), but not in amniotic fluid. 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 (see section **4.4. Special warnings and precautions for use**).

Lactation

Both doxorubicin and its main metabolite doxorubicinol pass into breast milk. The highest concentration in breast milk was measured 24 hours after administration. The relationship milk:plasma (AUC) was measured at 1,2 and 9,7 respectively for doxorubicin and doxorubicinol. It is possible that children who are being breast fed may sustain damage. Because of the potential for serious reactions in nursing infants from doxorubicin women should not breast feed 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 medicinal product is assumed not to influence the ability to drive a car or operate machines.

4.8. UNDESIRABLE EFFECTS

The following undesirable effects have been observed and reported when treated with doxorubicin with the following frequencies. Very common (affects more than 1 in 10 patients), Common (affects 1 to 10 of 100 patients), Uncommon (affect 1 to 10 of 1000 patients), Rare (affects 1 to 10 of 10000 patients), Very rare (affects less than 1 of 10000 patient), 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 leukaemia, acute myeloid leukaemia (AML)
Blood and Lymphatic System Disorders	
Very common	Leukopenia, neutropenia, anaemia, thrombocytopenia
Immune System Disorders	
Not known	Anaphylactic reaction
Metabolism and Nutrition Disorders	
Very common	Decreased appetite
Not known	Dehydration, Hyperuricaemia
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	
Not known	Embolism

Not known	Shock, Haemorrhage, Thrombophlebitis, Phlebitis, Hot flush
Gastrointestinal Disorders	
Very common	Mucosal inflammation/Stomatitis, Diarrhoea, Vomiting, Nausea
Common	Oesophagitis, Abdominal pain
Not known	Gastrointestinal haemorrhage, Gastritis erosive, Colitis, Mucosal discolouration
Skin and Subcutaneous Tissue Disorders	
Very common	Palmar-plantar erythrodysaesthesia 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	Amenorrhoea, 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

[a]For one to two days after administration.
[b]Reported in patients with early breast cancer receiving doxorubicin-containing adjuvant therapy (NSABP B-15 studie).

Blood and lymphatic system disorder:
A careful monitoring of leukocytes, erythrocytes and thrombocytes is required. Maximum myelosuppression will occur after appr. 2 weeks. Blood levels will usually normalize after 21 days. Dose reduction or prolongation of the dosing interval should be carried out if the blood levels are not normalized. Secondary acute myelogenous leukemia (AML) with or without pre-leukemic phase has been reported in individual patients treated with doxorubicin together with DNA-harming antineoplastic substances. Cases like these may have a short latency period (1-3 years).

Clinical consequences of myelosuppression may include fever, infections, sepsis/septicemia, septic shock, bleedings, tissue hypoxia or death. Intravenous antibiotic agents should be given in case of febrile neutropenia.

Cardiac disorder:
In long-term treatment the cardiac function has to be carefully monitored. Two different types of cardiac influence have been observed: Acute transient changes in the ECG occurring in direct association with or a few hours after administration. These are mostly reversible and have usually no clinical significance.

Cardiomyopathies, which are often dose dependent and serious in nature, may develop even a long

time after discontinuation of the treatment. These are often characterized by a reduction of the QRS complex and rapidly onsetting heart dilatation, which often does not respond to treatment with inotropic agents.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9. OVERDOSE

High single doses may cause myocardial damage within 24 hours and severe myelosuppression within approx. 2 weeks. Cardiac complications have been observed up to 6 months after administration of an overdose of anthracyclines.

Acute overdose of doxorubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (especially mucositis) and acute cardiac changes. Treatment in acute overdose should include hospital admission, intravenous antibiotic treatment, transfusions of platelets and granulocytes, and symptomatic treatment of gastrointestinal and cardiotoxic manifestations. Use of hematopoietic growth factors may be considered.

Chronic overdose, when the cumulative dose exceeds 550 mg/m^2, will increase the risk of cardiomyopathy and may cause heart failure. In this case the treatment should include digitalis, diuretics, peripheral vasodilators and ACE-inhibitors.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: ATC-code: L01D B01

Doxorubicin is a cytostatic antibiotic agent of the tetracycline type isolated from Streptomyces peucetius var. caesius.

Mechanism of action:

Not completely established. Intercalates in the DNA, and stabilizes the DNA-topoisomerase II-complex with subsequent inhibition of the synthesis of DNA and RNA. Triggers a cleavage of the DNA. Reacts with CP450 under formation of highly reactive and toxic free radicals. Interacts with cell membranes and influences the function of these.

Doxorubicin is mostly active in the S-phase of the cells. At low concentrations of doxorubicin the cells continue through the S-phase and die in G_2.

5.2. PHARMACOKINETIC PROPERTIES

Absorption:
Doxorubicin is not absorbed from the gastrointestinal tract. As the substance is very tissue

irritating it should be administered intravenously. When administered intravesically the absorption in the systemic circulation is minimal.

Distribution:
Following intravenous application, rapid distribution to extravasal compartments takes place, which is evidenced by the short distribution half-life (5 – 10 minutes). The steady-state volume of distribution is above 20 - 30 l/kg. Does not pass the blood-brain barrier in detectable amounts. Protein binding: Approx. 75%.

Biotransformation:
Metabolises fast in the liver. The most important metabolite, 13-OH doxorubicinol has a certain anti-tumour effect. Aglycones of doxorubicin and 13-OH-doxorubicinol are also formed.

Elimination:
In several patients with normal function of the liver and kidneys the plasma levels of doxorubicin go through a multiphasic course, with a terminal phase ($t1/2_{\gamma}$) of 20 – 48 hours. 13-OH-doxorubicinol has the same $t_{1/2}$ as doxorubicin. Plasma clearance is in the area of 8 - 20 ml/min/kg. Appr. 5 - 10% is secreted through the urine during the initial five days, while 40 - 50% is secreted through bile and faeces within seven days. Obesity, impaired liver function and increased plasma concentration of bilirubin will result in a slower secretion.

5.3. PRECLINICAL SAFETY DATA

LD50 for doxorubicin is, for mice and rats respectively, 21.9 and 12.5 mg/kg, and appr. 2.0 mg/kg for dogs. The main target organs following single administration was the hemolymphopoietic system, and in particular for dogs also the gastro-intestinal tract. Toxic effects following repeated dosing were investigated in rats, rabbits and dogs. The main target organs were the hemolymphopoietic system, the gastrointestinal tract, the kidneys, the liver and the reproductive organs in both females and males.

Both subacute and cardiotoxicity studies indicated that doxorubicin was cardiotoxic in all animal species tested. Like for other anthracyclines and cytotoxic drugs it has been found that doxorubicin is carcinogenic in rats.

The treatment of pregnant rats with doxorubicin prior to implantation caused an increase in the number of micronuclei in the blastocyst and an increase in the number of post implantation losses. The treatment of pregnant rats during the organogenesis leads to malformations in inner organs of the offspring. The treatment of pregnant rabbits with doxorubicin leads to an increased number of abortions, but not malformations.

Doxorubicin is genotoxic in most of the *in vitro* and in vivo tests which have been carried out.

A local safety study in dogs demonstrated that extravasal injection causes tissue necrosis.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Lactose, methyl parahydroxybenzoate (E218).

6.2. INCOMPATIBILITIES

Shall not be mixed with heparin or fluorouracil (e.g., in the same IV infusion bag or at the Y-site of an IV infusion line), as this will lead to precipitation. Until further data are available, it is not recommended to give doxorubicin in the same solution with other medicinal products. If concomitant therapy with doxorubicin and fluorouracil is required, it is recommended that the IV line be flushed between the administration of these drugs.

Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin.

6.3. SHELF LIFE

Pack (Nature & Content of Container)	**Shelf-life**	**Storage Conditions**
1's vial	24 Months	Store below 25°C

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25 °C.

6.5. NATURE AND CONTENTS OF CONTAINER

Vials from colourless glass, closed by Teflon covered stoppers from chlorobutyl rubber, sealed with an aluminium cap with a grey polypropylene washer.
Pack sizes: 1 × 10 mg and 1 × 50 mg.

Not all pack size may be marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Powder for solution for injection, 10 mg and 50 mg is dissolved in 5 and 25 ml of sterile water, respectively, or in sodium chloride solution for injection, 9 mg/ml. May be mixed with glucose solution for infusion, 50 mg/ml.

- Cytostatics should if possible be reconstituted in ventilated conditions. Surgical gloves and protective garb should be used. If there is no available ventilation, the protective equipment should be supplemented with mouth gauze and a facial mask or protective goggles.
- Onto each injection syringe a label shall be attached giving the name and amount of the substance.
- If air and surplus solution must be pressed out of the syringe before the injection, this is easily done against a sterile compress.
- Shall not get in contact with the skin. (Use protective gloves!)
- Waste which has been in contact with concentrates of cytostatic agents shall be handled according to the applicable rules for contaminated clinical waste (hence does not apply to glassware etc. which have contained diluted solutions of cytostatic agents in a volume of at least 500 ml)

It is important to check that the drip does not stop while the cytostatic agent is being injected. The needle should be inserted into the lower arm.

6.7. DRUG PRODUCT SPECIFICATIONS

Pfizer Specifications

7. REGISTRATION HOLDER/MARKETING AUTHORIZATION HOLDER:

Pfizer Pakistan Limited
12 Dockyard Road, West Wharf, Karachi

Name of the Manufacturing site	Address of site	Manufacturing step (if applicable)
Corden Pharma Latina S.p.A	Via Murillo, 7 04013 Sermoneta, Latina, Italy	Production, Packaging, Testing & Batch release

8. REGISTRATION / MARKETING AUTHORIZATION NUMBER:

Adriblastina Injection 10mg : License no. 002580

Adriblastina Injection 50mg : License no. 014606

9. DATE FROM WHICH MARKETING IS AUTHORIZED:

Adriblastina Injection 10mg : Reg. date: 4-Nov-1993
Adriblastina Injection 50mg : Reg. date: 22-Apr-1977

Adriblastina/LPD/PK-01
According to Norway SmPC dated October 11, 2023 & approved information in Pakistan

Marketed by:
Pfizer Pakistan Limited
*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*