Adriblastina®
Rapid Dissolution
Powder for Injection

PHARMACIA

doxorubicin hydrochloride

Adriblastina® (doxorubicin hydrochloride or adriamycin hydrochloride) is an antiblastic anthracycline antibiotic isolated at the Pharmacia Italia S.p.A. Research Laboratories from culture of Streptomyces peucetius var. caesius.
Adriblastina® Rapid Dissolution contains doxorubicin hydrochloride as a freeze-dried powder with lactose and methylhydroxybenzoate . It is soluble in water ***or saline***.

Biological activity
The mechanism of action of Adriblastina® is related to the ability of the antibiotic to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration by the antibiotic and its main localization is in the perinucleolar chromatin. Rapid inhibition of mitotic activity and nucleic acid synthesis have also been demonstrated together with the appearance of chromosomal aberrations.
Animal studies on Adriblastina® have shown that the cytotoxic agent is active in a spectrum of experimental tumours and is immunosuppressive. However, it does give rise to a variety of toxic effects such as cardiac toxicity in rabbits and rats, atrophy of testes in rats and dogs and myelosuppression in all the animal species tested.

Clinical Pharmacology
Pharmacokinetic studies have shown that intravenous administration of labelled Adriblastina® is followed by a rapid fall in plasma levels, accompanied, however, by slow urinary and biliary excretion. This is probably due to binding of the antibiotic to tissues. Urinary excretion, as determined by fluorimetric methods, accounts for approximately 5% of the administered dose in 5 days; biliary excretion is the major elimination route, with 40-50% of the administered dose recovered in the bile or faeces in seven days.
Impaired liver function causes slower excretion of the drug and, in consequence, increased accumulation in plasma and tissues. Adriblastina® does not cross the blood-brain barrier.

Indications
Adriblastina® 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 carcinoma, bone and soft tissue sarcomas, Hodgkin's and non-Hodgkin's lymphomas, neuroblastoma, Wilm's tumour, acute lymphoblastic leukaemia and acute myeloblastic leukaemia.

SAFETY

Contraindications
Hypersensitivity to doxorubicin or any other component of the product, other anthracyclines or anthracenediones.

Intravenous (i.v.) route:
- Persistent myelosuppresion
- Severe hepatic impairment
- Severe myocardial insufficiency
- Recent myocardial infarction
- Severe arrhytmias

Previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones.

Intravesical use:
- Invasive tumours that have penetrated the bladder wall
- Urinary infections
- Inflammation of the bladder

Warning and Precautions
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).
Cardiac Function: cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.
Early (i.e., Acute) Events: Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes.
Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, 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 doxrubicin 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. 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.

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 preleukemic phase, has been reported in patients treated with anthracyclines. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, 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.

Carcinogenesis & Mutagenesis, Impairment of Fertility (see Pregnancy and Lactation). Doxorubicin was genotoxic in a battery of in vitro or in vivo tests. An increase in the incidence of mammary tumors was reported in rats, and a trend for delay or arrest of follicular maturation was seen in female dogs.
In women, doxorubicin may cause infertility during the time of drug administration. Doxorubicin may cause amenorrhea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.
Doxorubicin was toxic to male reproductive organs in animal studies, producing testicular atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing doxorubicin treatment should use effective contraceptive methods

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.

Liver 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. Patients with severe hepatic impairment should not receive doxorubicin.

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 DOSAGE AND ADMINISTRATION, Instruction for Use/Handling).

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.

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

Additional Warnings and Precautions for Other Routes of Administration
Intravesical route. 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 catherization problems (e.g., uretheral 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.

Pregnancy and Lactation
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.

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Doxorubicin is secreted into breast milk. Women should not breastfeed while undergoing treatment with doxorubicin .

Adverse Events
The following adverse events have been reported in association with doxorubicin therapy:
Cardiovascular: sinus tachycardia, ECG abnormalities, tachyarrhythmias, atrio-ventricular and bundle branch block, asymptomatic reductions in left ventricular ejection fraction, congestive heart failure
Hematologic: leukopenia, neutropenia, anemia, thrombocytopenia, hemorrhage
Gastrointestinal: anorexia, nausea/vomiting, dehydration, mucositis/stomatitis, hyperpigmentation of the oral mucosa, esophagitis, abdominal pain, gastric erosions, gastrointestinal tract bleeding, diarrhea, colitis
Liver: changes in transaminase levels, hyperuricemia
Endocrine: amenorrhea, hot flashes, oligospermia, azoospermia
Ocular: conjunctivitis/keratitis, lacrimation
Skin: alopecia, local toxicity, rash/itch, skin changes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin ("radiation recall reaction"), urticaria, acral erythema
Vascular: phlebitis, thrombophlebitis, thromboembolism
Other: anaphylaxis, infection, sepsis/septicemia, acute lymphocytic leukemia, acute myelogenous leukemia, malaise/asthenia, fever, chills, shock
Urological: red coloration of urine for 1 to 2 days after administration

Interactions
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 Warnings & Precautions). The use of doxorubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment. Changes in hepatic function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

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

DOSAGE AND ADMINISTRATION
Adriblastina Rapid Dissolution is not active orally and must not be administered intramuscularly or intrathecally.
Doxorubicin is usually administered by intravenous injection. Intravesical and intra-arterial routes may be used as indicated. Intravesical administration has been found beneficial in the treatment of superficial bladder cancer as well as in the prophylaxis of tumour recurrence after transurethral resection. The intra-arterial route of administration has also been used to produce intense local activity with reduced general toxicity (see Additional Warnings and Precautions for other Routes of Administration).

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.
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.
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 Contraindications).

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

Intravesical Administration
Doxorubicin administered intravesically can be used for the treatment of superficial bladder tumours or as prophylaxis to reduce recurrence after trans-urethral resection. 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.

Presentation
Each vial contains 10 mg of doxorubicin hydrochloride as a freeze-dried powder and is accompanied by an ampoule containing 5 ml of Water for Injections.
Each via contains 50 mg of doxorubicin hydrochloride as a freeze-dried powder to be dissolved in 25 ml of physiological saline.
The reconstituted solution is stable for 24 hours at room temperature and for 48 hours under refrigeration (2°-8° C).

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/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.

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.

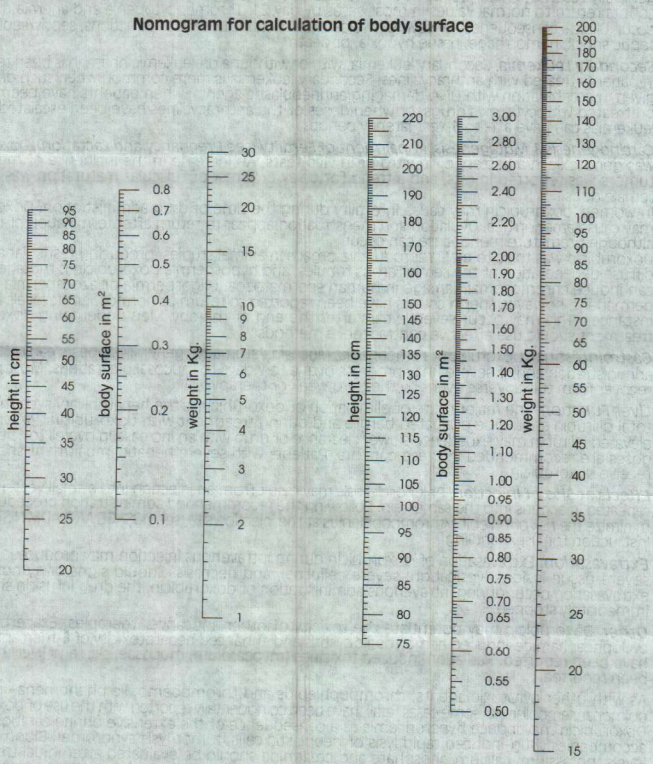
Instructions for Use/Handling
Preparation of the freeze-dried powder for intravenous administration. Dissolve powder in sodium chloride/water for injection. The vial contents are under negative pressure. To minimize aerosol formation during reconstitution; particular care should be taken when the needle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

Intravenous administration. 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 Warning and Precautions).

Intravesical administration. 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.

Protective measures. 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.

Nomogram for calculation of body surface

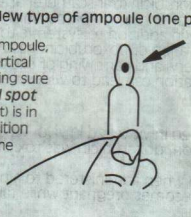


Read the body surface of the child or adult at the point where the straight line joining weight and height intersects the scale in the centre.

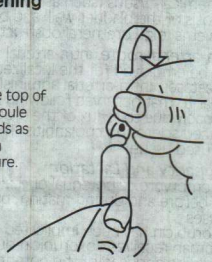
Instructions for the ampoule opening

Attention: New type of ampoule (one point cut ampoule)

To open the ampoule, hold it in a vertical position, making sure the ***coloured spot*** (one point cut) is in the same position as shown in the picture.



Push the top of the ampoule backwards as shown in the picture.



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