For the use of a oncologist or a Hospital or a Laboratory only

ADRIFAST

(Doxorubicin Hydrochloride Injection I.P.) (Lyophilised)

COMPOSITION

Adrifast 10

Each vial contains:

Doxorubicin Hydrochloride I.P.	10 mg
Methylparaben I.P.	1 mg

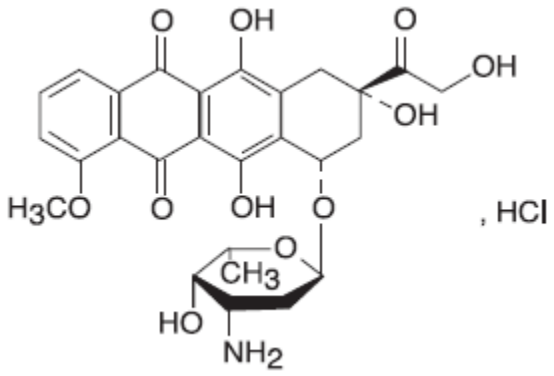
Adrifast 50

Each vial contains:

Doxorubicin Hydrochloride I.P.	50 mg
Methylparaben I.P.	5 mg

DESCRIPTION

Doxorubicin hydrochloride is (8S, 10S) - 10-[(3-amino-2, 3, 6-trideoxy -α-L-lyxohexo pyranosyl)oxy]-6,8,11-trihydroxy-8-hydroxyacetyl-1-methoxy-7,8,9,10-tetrahydro phthacene,12-dione hydrochloride. The molecular formula of Doxorubicin hydrochloride is $C_{27}H_{29}NO_{11}$. HCl and molecular weight is 580.0. The structuralformula is as follows:



Doxorubicin Hydrochloride is an orange-red, crystalline powder; hygroscopic. It is produced by growth of certain strain of Streptomyces coeruleorubidus or S. peucetius or obtained by any other means. It is soluble in water; slightly soluble in methanol; practically insoluble in chloroform, in ether and in other organic solvents.

CLINICAL PHARMACOLOGY

Mechanism of action:

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 affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases, and dehydrogenases generates 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.

Pharmacodynamics
Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Pharmacokinetics
Doxorubicin follows a multiphasic disposition after intravenous injection. Doxorubicin has demonstrated dose-independent Pharma cokinetics in the dose range of 30 to 70 mg/m^2.

Distribution:
The initial distribution half-life of approximately 5 minutes suggests rapid tissue uptake of doxorubicin, while its slow elimination from tissues is reflected by a terminal half-life of 20 to 48 hours. Steady-state distribution volume ranges from 809 to 1214 L/m^2 and is indicative of extensive drug uptake into tissues. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76 % and is independent of plasma concentration of doxorubicin up to 1.1 µg/mL. Doxorubicin was 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 µg/mL and AUC up to 24 hours was 9.0 µg.h/mL while the AUC for doxorubicin was 5.4 µg.h/mL. Doxorubicin does not cross the blood brain barrier.

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

Excretion
Plasma clearance is in the range 324 to 809 $mL/min/m^2$ 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. In urine, < 3% of the dose was recovered as DOX-OL over 7 days. Systemic clearance of doxorubicin is significantly reduced in obese women with ideal

body weight greater than 130%. There was a significant reduction in clearance without any change in volume of distribution in obese patients when compared with normal patients with less than 115% ideal body weight.

Pharmacokinetics in Special Populations

Pediatric:

Following administration of 10 to 75-mg/m^2 doses of doxorubicin to 60 children and adolescents ranging from 2 months to 20 years of age, doxorubicin clearance averaged 1443 ± 114 mL/min/m^2. Further analysis demonstrated that clearance in 52 children greater than 2 years of age (1540 mL/min/m^2) was increased compared with adults. However, clearance in infants younger than 2 years of age (813 mL/min/m^2) was decreased compared with older children and approached the range of clearance values determined in adults.

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/m^2 versus 433 mL/min/m^2). However, the terminal half-life of doxorubicin was longer in men compared to the women (54 versus 35 hours).

Hepatic Impairment:

The clearance of doxorubicin and doxorubicinol was reduced in patients with impaired hepatic function.

Renal Impairment:

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

INDICATIONS

Doxorubicin has been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin's disease, malignant lymphoma, and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types. Doxorubicin is also indicated for use as a component of adjuvant therapy in women with evidence of axillary lymph node involvement following resection of primary breast cancer.

CONTRAINDICATIONS

Patients should not be treated with doxorubicin if they have any of the following conditions:

- Bseline neutrophil count <1500 cells/mm^3;
- Severe hepatic impairment;
- Rcent myocardial infarction; severe myocardial insufficiency; severe arrhythmias;
- Pevious treatment with complete cumulative doses of doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthrax cenediones; or
- Hypersensitivity to doxorubicin, any of its excipients, or other anthracyclines or anthracenediones

DOSAGE AND ADMINISTRATION

When possible, to reduce the risk of developing cardiotoxicity in patients receiving doxorubicin after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, doxorubicin-based therapy should be delayed until the other agents have cleared from the circulation. Care in the administration of doxorubicin will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying 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 most commonly used dose schedule when used as a single agent is 60 to 75 mg/m^2 as a single intravenous injection administered at 21-day intervals. The lower dosage should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration.When used in combination with other chemotherapy drugs, the most commonly used dosage of doxorubicin is 40 to 60 mg/m^2 given as a single intravenous injection every 21 to 28 days.

Dose Modifications

Patients in one study dose modifications of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) to 75% of the starting doses for neutropenic fever/infection.

When necessary, the next cycle of treatment cycle was delayed until the absolute neutrophil count (ANC) was ≥1000 cells/mm^3 and the platelet count was ≥100,000 cells/mm^3 and nonhematologic toxicities had resolved.

Doxorubicin dosage must be reduced in case of hyperbilirubinemia as follows:

Plasma bilirubin concentration (mg/dL)	**Dosage reduction (%)**
1.2 - 3.0	50
3.1 - 5.0	75

Reconstitution Directions:
Reconstitute the 10 mg vial with 5 ml, 50 mg vial with 25 ml of sterile water for injection to give a final concentration of 2mg/ml. Bacteriostatic diluants not recommended.

It is recommended that doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of 0.9 % Sodium Chloride Injection or 5% Dextrose Injection. 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 dose should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an admini stration. A burning or stinging sensation may be indicative of perivenous infiltration and, if this occurs, the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly. Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin. Until specific compatibility data are available, it is not recommended that doxorubicin be mixed with other drugs. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Reconstituted Solution Stability
Reconstituted solution is stable for 24 hours at room temperature and for 48 hours in a refrigerator ($2^{o}C$-$8^{o}C$). Do not freeze after reconstitution. It should be protected from exposure to sunlight. Discard any unused solution.

Handling and Disposal

- The following protective recommendations are provided:
- 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 (prefereably 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.

Caregivers of pediatric patients receiving doxorubicin should be counseled to take precautions (such as wearing latex gloves) to prevent contact with the patient's urine and other body fluids for at least 5 days after each treatment.

WARNINGS AND PRECAUTIONS

Cardiac Toxicity

Special attention must be given to the risk of myocardial damage from cumulative doses of doxorubicin HCl. Acute left ventricular failure may occur with doxorubicin, particularly in patients who have received a total cumulative dosage of doxorubicin exceeding the currently recommended limit of 550 mg/m^2. Lower (400 mg/m^2) doses appear to cause heart failure in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide.

Prior use of other anthracyclines or anthracenodiones should be included in calculations of total cumulative dosage. Congestive heart failure or cardiomyopathy may be encountered after discontinuation of anthracycline therapy. Patients with a history of cardiovascular disease should be administered Doxorubicin only when the potential benefit of treatment outweighs the risk.

Cardiac function should be carefully monitored in patients treated with Doxorubicin. The most definitive test for anthracycline myocardial injury is endomyocardial biopsy. Other methods, such as echocardiography or multigated radionuclide scans, have been used to monitor cardiac function during anthracycline therapy. Any of these methods should be employed to monitor potential cardiac toxicity in patients treated with Doxorubicin. If these test results indicate possible cardiac injury associated with Doxorubicin therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

Infusion Reactions

Acute infusion-related reactions were reported in 7.1% of patients treated with Doxorubicin in the randomized ovarian cancer study. These reactions were characterized by one or more of the following symptoms: flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction resolved when the rate of infusion was slowed. In this study, two patients treated with Doxorubicin (0.8%) discontinued due to infusion-related reactions. In clinical studies, six patients with AIDS-

related Kaposi's sarcoma (0.9%) and 13 (1.7%) solid tumor patients discontinued Doxorubicin therapy because of infusion-related reactions.

Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

The majority of infusion-related events occurred during the first infusion. Similar reactions have not been reported with conventional doxorubicin and they presumably represent a reaction to the Doxorubicin liposomes or one of its surface components.

The initial rate of infusion should be 1 mg/min to help minimize the risk of infusio n reactions.

Myelosuppression

Because of the potential for bone marrow suppression, careful hematologic monitoring is required during use of Doxorubicin, including white blood cell, neutrophil, platelet counts, and Hgb/Hct. With the recommended dosage schedule, leukopenia is usually transient. Hematologic toxicity may require dose reduction or delay or suspension of Doxorubicin therapy. Persistent severe myelosuppression may result in superinfection, neutropenic fever, or hemorrhage. Development of sepsis in the setting of neutropenia has resulted in discontinuation of treatment and, in rare cases, death.

Doxorubicin may potentiate the toxicity of other anticancer therapies. In particular, hematologic toxicity may be more severe when Doxorubicin is administered in combination with other agents that cause bone marrow suppression.

In patients with relapsed ovarian cancer, myelosuppression was generally moderate and reversible. In the three single-arm studies, anemia was the most common hematologic adverse reaction (52.6%), followed by leukopenia (WBC< 4,000 mm^3; 42.2%), thrombocytopenia (24.2%), and neutropenia (ANC <1,000; 19.0%). In the randomized study, anemia was the most common hematologic adverse reaction (40.2%), followed by leukopenia (WBC <4,000 mm^3; 36.8%), neutropenia (ANC <1,000; 35.1%), and thrombocytopenia (13.0%).

In patients with relapsed ovarian cancer, 4.6% received G-CSF (or GM-CSF) to support their blood counts.

For patients with AIDS-related Kaposi's sarcoma who often present with baseline myelosuppression due to such factors as their HIV disease or concomitant medications, myelosuppression appears to be the dose-limiting adverse reaction at the recommended dose of 20 mg/m^2 . Leukopenia is the most common adverse reaction experienced in this population; anemia and thrombocytopenia can also be expected. Sepsis occurred in 5% of patients; for 0.7% of patients the event was considered possibly or probably related to Doxorubicin. Eleven patients (1.6%) discontinued study because of bone marrow suppression or neutropenia.

Table 10 presents data on myelosuppression in patients with multiple myeloma receiving Doxorubicin and bortezomib in combination.

Hand-Foot Syndrome (HFS)
In the randomized ovarian cancer study, 50.6% of patients treated with Doxorubicin at 50 mg/m^2 every 4 weeks experienced HFS (developed palmar-plantar skin eruptions characterized by swelling, pain, erythema and, for some patients, desquamation of the skin on the hands and the feet), with 23.8% of the patients reporting HFS Grade 3 or 4 events. Ten subjects (4.2%) discontinued treatment due to HFS or other skin toxicity. HFS toxicity grades are described above.

Among 705 patients with AIDS-related Kaposi's sarcoma treated with Doxorubicin at 20 mg/m^2 every 2 weeks, 24 (3.4%) developed HFS, with 3 (0.9%) discontinuing.

In the randomized multiple myeloma study, 19% of patients treated with Doxorubicin at 30 mg/m^2 every three weeks experienced HFS.

HFS was generally observed after 2 or 3 cycles of treatment but may occur earlier. In most patients the reaction is mild and resolves in one to two weeks so that prolonged delay of therapy need not occur. However, dose modification may be required to manage HFS. The reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

Radiation Recall Reaction
Recall reaction has occurred with Doxorubicin administration after radiotherapy.

Fetal Mortality
Pregnancy Category D
Doxorubicin can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. 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. If pregnancy occurs in the first few months following treatment with Doxorubicin, the prolonged half-life of the drug must be considered. Women of childbearing potential should be advised to avoid pregnancy during treatment with Doxorubicin.

Toxicity Potentiation
The doxorubicin in 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 with the conventional formulation of doxorubicin HCl. Radiation-induced toxicity to the myocardium, mucosae, skin, and liver have been reported to be increased by the administration of doxorubicin HCl.

Monitoring: Laboratory Tests
Complete blood counts, including platelet counts, should be obtained frequently and at a minimum prior to each dose of Doxorubicin.

Secondary Oral Neoplasms
Secondary oral cancers, primarily squamous cell carcinoma, have been reported from post-marketing experience in patients with long-term (more than one year) exposure to Doxorubicin. These malignancies were diagnosed both during treatment with Doxorubicin and up to 6 years after the last dose. Examine patients at regular intervals for the presence of oral ulceration or with any oral discomfort that may be indicative of secondary oral cancer.

The altered pharmacokinetics and preferential tissue distribution of liposomal doxorubicin that contributes to enhanced skin toxicity and mucositis compared to free doxorubicin may play a role in the development of oral secondary malignancies with long-term use.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) has been reported in patients treated with doxorubicin - containing combination chemotherapy regimens. Pediatric patients treated with doxorubicin or other topoisomerase II inhibitors are at risk for developing acute myelogenous leukemia and other neoplasms. Doxorubicin was mutagenic in the in vitro Ames assay, and clastogenic in multiple in vitro assays and the

In vivo mouse micronucleus assay
Doxorubicin decreased fertility in female rats at the doses of 0.05 and 0.2 mg/kg/day (about 1/200 and 1/50 the recommended human dose on a body surface area basis) when administered from 14 days before mating through late gestation period. Doxorubicin is mutagenic as it induced DNA damage in rabbit spermatozoa and dominant lethal mutations in mice. Therefore, doxorubicin may potentially induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia were evidenced in men treated with doxorubicin, mainly in combination therapies. Men undergoing doxorubicin treatment should use effective contraceptive methods. Doxorubicin was toxic to male reproductive organs in animal studies, producing testicular atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia.

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. Recovery of menses is related to age at treatment.

DRUG INTERACTIONS
Doxorubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy, and/or toxicity. Toxicities associated with doxorubicin, especially

hematologic and gastrointestinal events, may be increased when doxorubicin is used in combination with other cytotoxic drugs.

Paclitaxel:
Co-administration of paclitaxel infused over 24 hours followed by doxorubicin administration over 48 hours resulted in a significant decrease in doxorubicin clearance with more profound neutropenic and stomatitis episodes than the reverse sequence of administration.

Progesterone:
In a published study, progesterone was given intravenously to patients with advancedmalignancies (ECOG PS < 2) at high doses (up to 10 g over 24 hours) concomitantly with a fixed doxorubicin dose (60 mg/m^2) via bolus injection. Enhanced doxorubicin - induced neutropenia and thrombocytopenia were observed.

Verapamil:
One study on the effects of verapamil on the acute toxicity of doxorubicin in mice revealed higher initial peak concentrations of doxorubicin in the heart with a higher incidence and severity of degenerative changes in cardiac tissue resulting in a shorter survival.

Cyclosporine:
The addition of cyclosporine to doxorubicin may result in increases in AUC for both doxorubicin and doxorubicinol possibly due to a decrease in clearance of 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 doxorubicin alone. Coma and/or seizures have also been described.

Dexrazoxane:
The concurrent use of the cardioprotectant, dexrazoxane, with the initiation of a regimen of fluorouracil, doxorubicin, and cyclophosphamide (FAC) was associated with a lower tumor response rate. Later initiation of dexrazoxane (after administration of a cumulative doxorubicin dose of 300 mg/m^2 of doxorubicin had been given as a component of FAC) was not associated with a reduction in chemotherapy activity. Dexrazoxane is only indicated for use in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and are continuing with doxorubicin therapy.

Cytarabine:
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 intravenous push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

Sorafenib:
In clinical studies, both an increase of 21% and 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.

Cyclophosphamide:
The addition of cyclophosphamide to doxorubicin treatment does not affect exposure to doxorubicin, but may result in an increase in exposure to doxorubicinol, a metabolite. Doxorubicinol only has 5% of the cytotoxic activity of doxorubicin. Concurrent treatment with doxorubicin has been reported to exacerbate cyclophosphamide-induced hemorrhagic cystitis. Acute myeloid leukemia has been reported as a second malignancy after treatment with doxorubicin and cyclophosphamide.

Miscellaneous:
Phenobarbital increases the elimination of doxorubicin; phenytoin levels may be decreased by doxorubicin; Streptozocin may inhibit hepatic metabolism of doxorubicin; saquinavir in combination with cyclophosphamide, doxorubicin, and etoposide increased mucosal toxicity in patients with HIV-associated non-Hodgkin's lymphoma; and administration of live vaccines to immunosuppressed patients including those undergoing cytotoxic chemotherapy may be hazardous.

Laboratory Tests
Initial treatment with doxorubicin requires observation of the patient and periodic monitoring of complete blood counts, hepatic function tests, and left ventricular ejection fraction. Abnormalities of hepatic function tests may occur. Like other cytotoxic drugs, doxorubicin may induce hepaor-lysis syndrome" and hyperuricemia in patients with rapidly growing tumors. 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.

ADVERSE REACTIONS

- Cardiac Toxicity
- Infusion reactions
- Myelosuppression
- Hand-Foot syndrome
- Secondary Oral Neoplasms

The most common adverse reactions observed wit Doxorubicin are asthenia, fatigue, fever, nausea, stomatitis, vomiting, diarrhea, constipation, anorexia, hand-foot syndrome, rash and neutropenia, thrombocytopenia and anemia.

Adverse Reactions in Clinical Trials
Patients with ovarian cancer
Incidence 1% to 10%

Cardiovascular: vasodilation, tachycardia, deep thrombophlebitis, hypotension, cardiac arrest.

Digestive: oral moniliasis, mouth ulceration, esophagitis, dysphagia, rectal bleeding, ileus.

Hemic and Lymphatic: ecchymosis.

Metabolic and Nutritional: dehydration, weight loss, hyperbilirubinemia, hypokalemia, hypercalcemia, hyponatremia.

Nervous: somnolence, dizziness, depression.

Respiratory: rhinitis, pneumonia, sinusitis, epistaxis.

Skin and Appendages: pruritus, skin discoloration, vesiculobullous rash, maculopapular rash, exfoliative dermatitis, herpes zoster, dry skin, herpes simplex, fungal dermatitis, furunculosis, acne.

Special Senses: conjunctivitis, taste perversion, dry eyes.

Urinary: urinary tract infection, hematuria, vaginal moniliasis.

The following additional adverse reactions were observed in patients with AIDS-related Kaposi's sarcoma.
Incidence 1% to 5%
Body as a Whole: headache, back pain, infection, allergic reaction, chills.

Cardiovascular: chest pain, hypotension, tachycardia. *Cutaneous:* herpes simplex, rash, itching. *Digestive:* mouth ulceration, anorexia, dysphagia. *Metabolic and Nutritional:* SGPT increase, weight loss, hyperbilirubinemia. *Other:* dyspnea, pneumonia, dizziness, somnolence.

Incidence Less Than 1%
Body as a whole: sepsis, moniliasis, cryptococcosis.

Cardiovascular: thrombophlebitis, cardiomyopathy, palpitation, bundle branch block, congestive heart failure, heart arrest, thrombosis, ventricular arrhythmia.

Digestive: hepatitis.

Metabolic and Nutritional Disorders: dehydration

Respiratory: cough increase, pharyngitis.

Skin and Appendages: maculopapular rash, herpes zoster.

Special Senses: taste perversion, conjunctivitis.

Post Marketing Experience
The following additional adverse reactions have been identified during post approval use of Doxorubicin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Musculoskeletal and Connective Tissue Disorders: rare cases of muscle spasms.

Respiratory, Thoracic and Mediastinal Disorders: rare cases of pulmonary embolism (in some cases fatal).

Hematologic disorders: Secondary acute myelogenous leukemia with and without fatal outcome has been reported in patients whose treatment included Doxorubicin.

Skin and subcutaneous tissue disorders: rare cases of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Secondary oral neoplasms:

OVERDOSAGE
Acute overdosage with doxorubicin enhances the toxic effect of mucositis, leukopenia, and thrombocytopenia. 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. Treatment consists of vigorous management of congestive heart failure with digitalis preparations, diuretics, and after-load reducers such as ACE inhibitors. Caution should be exercised to prevent inadvertent overdosage.

EXPIRY DATE
Do not use later than expiry date.

STORAGE
Store at a temperature not exceeding $30^{o}C$.
Protect from light and moisture. Keep out of reach of children.

PRESENTATION
ADRIFAST is available as sterile single use Lyophilised injection in a vial containing Doxorubicin

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.
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