Urine should be inactivated by decolorizing it with 10 mL or more of sodium hypochlorite solution (household)

Warning:
As with all parenteral drug products, i.v admixtures should be inspected visually for clarity , particulate matter, precipitate. discoloration and leakage prior to administration. Solution showing such should not be used.

Incompatibilities:
Unless specific compatibility data are available . the mixing of doxorubicin solutions with other drugs is not recommended. Pre-cipitation occurs with 5-fluorouracil and heparin.

Guidelines for Safe Preparation and Handling:
Preparation and Handling : 1. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet -Class II). 2. Personal preparing doxorubicin solutions should wear PVC gloves , safety glasses and protective clothing such as disposable gowns and masks. If doxorubicin contacts the skin or mucosa, the area should be washed with soap and water immediately. 3. Personnel regularly involved in the preparation and handling of antineoplastics should have blood examinations on a regular basis.

Disposal:
1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.
2. All needles, syringes, vials and other materials which have come in contact with doxorubicin should be segregated in plastic bags, sealed, and marked as hazardous waste. Incinerate at 1 000 C or higher. Sealed containers may explode if a tight seal exists.
3. If incineration is a not available, doxorubicin may be detoxified by adding sodium hypochlorite solution (household bleach) to the vial, in sufficient quantity to decolorize the doxorubicin care being taken to vent the vial to avoid pressure build-up of the chlorine gas which is generated. Dispose of detoxified vials in a safe manner.

Direction for Reconstitution: D-Rubicin 10mg and 50mg vials should be reconstituted with 5mL and 25mL respectively of water for injection. The reconstituted solution stored at room temperature may be used within 24 hours.

How Supplied:
D-RUBICIN-10 Injection: Single dose vial containing Doxorubicin HCl USP 10mg, Packed in unit carton

D-RUBICIN-50 Injection: Single dose vial containing Doxorubicin HCl USP 50mg, Packed in unit carton

Storage:
Store below 25°C . Keep away from direct sunlight
Keep out of the reach of children.

ڈی۔روبیسن انجکشن

ڈوکسوروبیسن ہائیڈروکلورائیڈ یوایس پی 10/50 ملی گرام

دھوپ، گرمی اور نمی سے محفوظ رکھیں۔ 25° سینٹی گریڈ سے کم درجہ حرارت پر سٹور کریں۔
تمام ادویات بچوں کی پہنچ سے دور رکھیں۔ ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

Revised: Jan.2017

Manufactured by :
Pharmedic Laboratories (Pvt) Limited.
16 Km. Multan Road, Lahore - Pakistan
Phone : (92-42) 37511861 - 65, Fax : (92-42) 37511396

Injection
D-RUBICIN
DOXORUBICIN HCL USP
10mg / 50mg

Clinical Pharmacology:
The precise mechanism(s) of the antineoplastic action of doxorubicin is not fully understood. Experimental evidence indicates that doxorubicin forms a complex with DNA by intercalation between base pairs, causing inhibition of DNA synthesis and DNA-dependent RNA synthesis by the resulting template disordering and steric obstruction. Doxorubicin also inhibits protein synthesis. Doxorubicin is active throughout the cell cycle including interphase. Doxorubicin also has immunosuppressive activity.

Pharmacokinetics:
Absorption: Doxorubicin is not stable in gastric acid and animal studies indicate that it is not absorbed from the gastrointestinal track. Distribution: Doxorubicin is widely distributed in the plasma and in tissues. As early as 30 seconds after i.v administration doxorubicin is present in the liver, lungs hearty and kidneys Doxorubicin is absorbed by cells and binds to cellular components, particularly to nucleic acids. Doxorubicin does not cross the blood-brain barrier or achieve a measurable concentration in the CSF.

Elimination: Plasma concentrations of doxorubicin and its metabolites decline in a triphasic manner. In the first phase, doxorubicin is rapidly metabolized, presumably by a first-pass effect through the liver. It appears that most of this metabolism is completed before the entire dose is administered. Doxorubicin and its metabolites are rapidly distributed into the extra vascular compartment with plasma half-life of approximately 0.6 hours for doxorubicin and 3.3 hours for the metabolites. This is followed by relatively prolonged plasma concentrations of doxorubicin and its metabolites, probably resulting from tissue binding. During the second phase , the plasma half-life of doxorubicin is 16.7 hours and that of its metabolites is 31.7 hours. Patients with impaired hepatic function have prolonged and elevated plasma concentrations of both the drug and its metabolites. Plasma protein binding is approximately 50%.

Doxorubicin is metabolized in the liver and other tissues by an Aldo-kato reductase enzyme, yielding doxorubicin (adriamycinol) the major metabolite which has antineoplastic activity. Other metabolites which are therapeutically inactive include doxorubicin (adriamycinone), aglycones and conjugates. More than 20 % of the total drug in plasma is present as metabolites as soon as 5 minutes after a dose, 70% in 30 minutes.75% in 4 hours, and 90% in 24 hours.

Doxorubicin is excreted predominantly in bite. Ten to 20% of a single dose is excreted in feces in 24 hors, and 40 to 50 % of a dose is excreted in bile or feces within 7 days. About 50% of the drug in bile is unchanged drug, 23% is doxorubicin , and the remainder is other metabolites including aglycones and conjugates. About 4 to 5 % of th administered drug is excreted in urine after 5 days. principally as unchanged doxorubicin . It appears that very little further urinary excretion of the drug occurs after 5 days.

Indications and Clinical Uses:
Doxorubicin has been used successfully both as a single agent and also in combination with other approved cancer chemotherapeutic agents to produce regression in neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilm's tumor neuroblastomas, soft tissue sarcomas bone sarcomas, breast carcinoma, gynecologic carcinomas, testicular carcinomas, bronchogenic carcinoma, lymphomas of both Hodgkin and nonHodgkin types, thyroid carcinoma, bladder carcinomas, squamous cell carcinoma of the head and neck, hepatic and gastric carcinoma. Doxorubicin has also been used by instillation into the bladder for the topical treatment of superficial bladder tumors.

A number of other solid tumors have also shown some responsiveness to doxorubicin alone or in combination with other drugs (see Dosage). Studies to date have shown malignant melanoma, kidney carcinoma, large bowel carcinomas, brain tumors and metastases to the CNS no to be significantly responsive to doxorubicin therapy.

Contra-Indications:
Doxorubicin therapy should no be started in patients who have marked myelosuppression induced by previous treatment with other antiblastic agents or by radiotherapy. Conclusive data are not available on pre existing heart disease as a cofactor for increased risk of doxorubicin-induced cardiac toxicity. Preliminary data suggest that in such cases cardiac toxicity may occur at doses lower than the recommended cumulative limit. It is therefore not recommended that doxorunicin be started in such cases. Doxorunicin treatment is contraindicated in patients who have received previous treatment with complete cumulative doses of doxorubicin, daunorubicin or other anthracyclines and anthracenes.

Use in Pregnancy and Lactation:
The safe use of doxorubicin in pregnancy has not been established. Doxorubicin is embryo toxic and theratogenic in rats and embryo toxic and abortifacient in rabbits. Therefore, the benefits to the pregnant patient should be carefully weighed against the potential toxicity to fetus and embryo. The possible adverse effects on fertility in males and females in humans or experimental animals have not been adequately evaluated. Mothers should be advised no to breast-feed while undergoing chemotherapy with doxorubicin.

Precautions:
Initial treatment with doxorubicin required close observation of the patient and extensive laboratory monitoring. Like other cytotoxic drugs, doxorubicin may induce hyperuricemia secondary to rapid lysis of neoplastic cells, particularly in patients with leukemia. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem. Doxorubicin may impart a red coloration to the urine for 1 to 2 days after administration and patients should be advised to expect this during active therapy.

Adverse Reaction:
Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity (see Warning) Other reactions reported are: Cutaneous : Reversible complete alopecia occurs in most cases. Hypergifmentation of nailbeds and dermal creases. primarily in children, have been reported in a few cases. Recall of skin reaction due to prior radiotherapy has occurred with doxorubicin administration.

Gastrointestinal: Acute nausea and vomiting occurs frequently and may be severe. Mucositis (stomatitis and esophagitis) may occur 5 to 10 days after administration. Anorexia and diarrhea have been occasionally reported.

Vascular: Phlebosclerosis has been reported especially when small veins are used or a single vein is used for repeated administration. Facial flushing may occur if the injection is given too rapidly.

Local: Severe cellulitis, vesication and tissue necrosis will occur if doxorubicin is extravasated during administration. Erythematous streaking along the vein proximal to the site of the injection has been reported (see Dosage)

Bladder, local : Instillation of doxorubicin into the bladder may cause pain, hemorrhage and occasionally decreased bladder capacity.

Hypersensitivity: Fever, chills and urticaria have been reported occasionally. Anaphylaxis may occur.

Other : Conjunctivitis and lacrimation occur rarely.

Symptoms and Treatment Of Overdose:
Acute over dosage with doxorubicin enhances the toxic effects of mucositis, leukopenia and thrombopenia. Treatment of acute over dosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

Chronic over dosage with cumulative doses exceeding 500 mg/m2 increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. The use of peripheral vasodilators has been recommended.

Dosage and Administration:
The most commonly used dosage schedule is 60 to 75 mg/m2 as a single i.v injection administered at 21-day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dose schedule is weekly doses of 20 mg/m2 which has been reported to produce lower incidence of congestive heart failure. 30 mg/m2 on each of 3 successive days repeated every 4 weeks has also been used. Doxorubicin dosage must be reduced if the bilirubin is elevated as follows: serum bilirubin 1.2 to 3.0 mg/dL - give ½ normal dose, > 3 mg/dL - give 1/4 normal dose.

When doxorubicin is intravesically instilled for the treatment of superficial bladder carcinomas, the ususal dose employed ranges from 50 to 80 mg in 50 to 100 mL of 0.9% Sodium Chloride Injection USP with a contact time of 1 to 2 hours. Care should be taken to ensure that the tip of the catheter is in the bladder lumen before instilling the doxorubicin solution. Instillation is repeated weekly for 4 weeks and subsequently at monthly intervals. Therapy may continue for 1 year or longer as no significant systematic toxicity has been reported. Care should be exercised in the handing and disposal of the voided urine. (Refer to Guidelines for Safe Preparation and Handing). PVC gloves should be worn and the