Zuvidox

Doxorubicin Injection IP (Lyophilized Powder)

Composition:

Zuvidox -10

Each vial contains:

Doxorubicin HCL IP 10 mg.

Lactose IP 50 mg.

Zuvidox -50

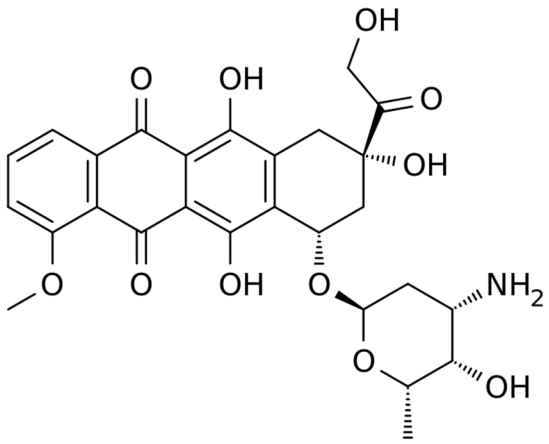
Doxorubicin HCl IP 50 mg.

Lactose IP 250 mg.

Description :

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of Streptomyces peucetius var. Caesisus. Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ringatom 7 to an amino sugar, daunosamine. Chemically, doxorubicin hydrochloride is : (8S, 10S)-10-[(3-Amino2,3,6-trideoxy-a-L-lyxo-hexopyranosyl)-oxy]-8-glycology]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy5,12-naphthacenedione hydrochloride [25316-40-9]

The structural formula is as follows:



Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic but the saturated end of the ring

system contains abundant hydroxyl groups adjacent to the amino sugar, producing a hydrophilic centre. The molecule is amphoteric, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. It binds to cell membrances as well as plasma proteins. Zuvidox (doxorubicin hydrochloride Injection, IP) is for intravenous use only. It is available in 10 mg and 50 mg single dose vials as a red-orange lyophilized, sterile powder with added lactose (anhydrous), 50 mg and 250 mg, respectively.

MACHANISM OF ACTION:

There are several hypothesis concerning the mode of action of doxorubicin. The best documented mechanism is its ability to interact with DNA, presumably by interaction of the planner aglycone, moiety between two adjacent base pairs. This may result inhibition of DNA repair mechanism.

Another mechanism of action may be binding to cell membranes, resulting in altered permeability properties. A third mechanism involves formation of free radicals. Reduction of doxorubicin may result in formation of semiquinolone redicals, which in turn give rise to variety or oxygen species

superoxide and hydroxyl radicals and hydrogen peroxide) These reactive species can damage cell membranes and organelles but may also interact with DNA. There is evidence that free redical formulation may have a role in the mutagenicity and cardiotoxicity of doxorubicin.

PHARMACOKINETICS:

The intravenous administration of doxurubicin is followed by rapid plasma clearance and significant tissue binding. After doses of 30-60 mg/m2 initial plasma concentrations are approximately 2-6 um Doxorubicin Kinetics are generally adequately described a three compartmental Kinetics model, with corresponding half lives 11/12 a/4 -8 min, 11/2b 0.7-1.6 h and t ½ g t of 25-35 h. volume of distribution is high, ranging from 800-3500/Lm2 .Doxorubicin is metabolized extensively. Three types of metabolic reactions occur Ketoreduction, cleavage reaction with aglycone formation, and conjugation, some metabolities (e.g. 7 hydroxyaglycones) have been correlated with Cardiotoxicity in humans. Elimination of doxorubicin, unchanged or metabolized occurs primarily via the liver and billiary system. Billiary excertion may be as high as 40.50% in 5-7 days. Approximately 10% of the total dose administered is excreted in the urine, in about 5-7 days.

INDICATIONS :

Doxorubicin is indicated in the treatment of acute leukemia, soft tissue and bone sarcomas, breast cancer, overian cancer, Hodgkin;s and non Hodgkin's lymphomas, small cell lung cancer, gastric carcinoma and bladder carcinoma.

DOSAGE AND ADMINISTRATION:

The most commonly used dosage schedule is 60-70 mg/m2 as a single intravenous administered at 21 days interval. Lower dose may be required in patients with inadequate marrow reserves.

An alternative dosage schedule of 20 mg /m2 weekly has been reported to produce a lower incidence of congestive heart failure. Doxorubicin dosage should be reduced if the bilirubin is elevated as follow; serum bilirubin 1.3 to 3.0 mg/dl give ½ normal dose, bilirubin > 3.0 mg/dl give 1/4 normal dose .

Reconstitution: Zuvidox 10 and 50 vials should be reconstituted with 5 mL and 25 mL. respectively, of Sodium Chloride Injection, USP /IP (0.9%) to give a final concentration of 2 mg/ML of doxorubicin Hydrochloirde. Bacteriostatic diluents are not recommended. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and under normal room light and 15 days under refrigeration 2°-8°C(36°-46°F). It should be protected from exposure to sunlight and any unused solution should be discarded.

Warning and precautions:

Special attention must be given to the cardiac toxicity exhibited by doxorubicin.

Although uncommon, acute left ventricular failure has occurred particularly in patients who have received total dosage of the drug exceeding the currently recommended limit of 550 g/m2. The limit appears to be lower in patients who received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. The total dose of doxorubicin administered to the individual patients should also take into account. Previous or concomitant therapy with related compounds such as Daunorubicin. Congestive heart failure and / or cardiomyopathy may be encountered several weeks after discontinuation of doxorubicin therapy. Cardiac failure is often not favorably affected by presently known edical or physical therapy for cardiac support. Early Clinical diagnosis of drug induced heart failure appears to be essential for successful treatment with digitals. Diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent ECG changes, A base line ECG and ECGs performed prior to each dose or course after 300 mg/m2 cumulative dose has been given is suggested. Transient ECG changes consisting of T-wave flattering S-T depression and arrhythmias lasting up to two weeks after a dose or course of doxorubicin are presently not considered indications for suspension of doxorubicin therapy. Doxorubicin cardiomyopathy has been reported to be associated with a persistent reduction in the voltage of the ORS wave a prolongation of the systolic time interval and a reduction of the ejection fraction as determined by echocardiography or radionuclide angiography. None of these tests have yet been confirmed to consistently identity those individual patients that are approaching their maximally tolerated cumulative dose of doxorubicin. If test result indicate change in cardiac function associated with doxorubicin the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage. Acute life threatening arrhythmias have been reported to occur during or within a few hours after doxorubicin administration.

There is a high incidence of bone marrow depression, primarily of leukocytes, requiring carefully hematologic monitoring with the recommended dose schedule, leukopenia is usually transient, reaching its nadir at 10-14 days after treatment with recovery usually occurring by the 21st day.

White blood cell counts as low as 1,000/mm3 are to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored since they may also be depressed Hematologic toxicity may require dose reduction or suspension or delay of doxorubicin therapy. Persistent severe myelosuppression may reuslt in superinfection or haemorrhage

Toxicity to recommended doses of doxorubicin is enhanced by hepatic impairment, therefore prior to the individual dosing evaluation of hepatic function is recommend using conventional clinical laboratory test,

such as SGOT, SGPT, alkaline phosphatase and bilirubin (See Dosage and Administration) Necrotizing colitis manifested by typhilitis (cecal inflammation bloody stools and severe and sometimes fatal infection have been associated with a combination of doxorubicin given I.V. Push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

On intravenous administration of doxorubicin extravasation any occur with or without an accompanying stinging or burning sensation and even if blood returns well on aspiration of the infusion needle. If any signs or symptoms and extravasation have occurred the injection or infusion should be immediately terminated and restarted in another vein. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained. Early wide exacission of the involved area should be considered.

Initial treatment with doxorubicin requires close observation of the patient and extensive laboratory monitoring. It is recommended, therefore, that patients, be hospitalized at least during the first phase of the treatment like other cytotoxic drugs, doxorubicin may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use supportive and pharmacologic measures as might be necessary to control this problem. Doxorubicin imparts are coloration to the urine 1-2 days after administration and patients should be advised to expect this during active therapy.

USE DURING PREGNANCY AND LACTATION :

Doxorubicin can cause fetal harm when administered to a pregnant woman. Doxorubicin was teratogenic and embryotoxic at doses of 0.8 mg/kg/day and greater (about 1/13 the recommended human dose on a body surface area basis) when administered during the period of organogenesis in rats. Teratoginicity and embryotoxicity were also seen using discrete periods of treatment. The most susceptible was the 6 to 9 days gestation period at doses of 1.25 mg/kg/day and greater Characteristic malformations included esophageal and intestinal atresia tracheoesophageal fistula, hypoplasia of the urinary bladder, and cardiovascular anomalies, Doxorubicin was embryotoxic (increase in embryofetal deaths) and abortifiacient at 0.4 mg/kg/day (about 1/14 the recommended human dose on a body surface area basis) in rabbits when administered during the period of organogenesis.

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. Women of childbearing age should be advised to avoid becoming pregnant.

PRECAUTIONS

Doxorubicin is not an anti-microbial agent. Doxorubicin is emetigenic. Antiemetics may reduce nausea and vomiting; prophylactic use of antiemetics should be considered before administration of doxorubicin, particularly when given in conjunction with other emetigenic drugs. Doxorubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving doxorubicin 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. Physicians should avoid doxorubicin-based therapy for up to 24 weeks after stopping trastuzumab when possible. If doxorubicin used before this time, careful monitoring of cardiac function is recommended

Patients should be informed of the expected adverse effects of doxorubicin, including gastrointestinal symptoms (nausea, vomiting, diarrhea, and stomatitis) and potential neutropenic complications. Patients should consult their physician if vomiting, dehydration, fever, evidence of infection, symptoms of CHF, or injection-site pain occurs following therapy with doxorubicin. Patients should be informed that they will almost certainly develop alopecia. Patients should be advised that their urine may appear red for 1 to 2 days after administration of doxorubicin and that they should not be alarmed. Patients should understand that there is a risk of irreversible myocardial damage associated with treatment with doxorubicin, as well as a risk of treatment-related leukemia. Because doxorubicin may induce chromosomal damage in sperm, men undergoing treatment with doxorubicin should use effective contraceptive methods. Women treated with doxorubicin may develop irreversible amenorrhea, or premature menopause.

ADVERSE EFFECTS:

Myelosuppression and cardiotoxicity are the dose limiting toxicities. Other adverse reactions are as follows:

Cutaneous:

Reversible and complete adopecia may occur Hyperpigmentation of nailbeds and dermal creases, primarily in children, and onycholysis in a few cases has been reported. Recail of skin reaction due to prior radiotherapy may occur with doxorubicin administration.

Gastorintestinal:

Acute nausea and vomiting occurs frequently which may be alleviated by antimetic therapy. Mucositis (stomatitis and esophagills) may occur 5-10 days after administration and may be severe with dose regimen consisting of administration of doxorubicin on three consecutive days. The effect may lead to ulceration and represent a site of origin for severe infection. Ulceration and necrosis of the colon, especially the cecum may occur leading to bleeding or severe infections, which can be fatal. This has been reported in ANLL patients being treated with a three day course inclusive of doxorubicin combined with cytarabine. Anorexia and diarrhoea have been occasionally reported.

Vascular:

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

Local :

Severe cellulities, 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.

HYPERSENSITIVITY:

Fever, Chills and urticaria have been reported occassionally. Anaphylaxis may occur. A case of apparent cross sensitivity to lincomycin has been reported.

Other Conjunctivities and lacrimation occur rarely

DRUG INTERACTIONS:

Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide induced cystitis and enhancement of 6-mercaptopurine hepatotoxicity have been reported. Radiation induced toxicity to the myocardium, mucosae skin and liver has been reported to be increased by the administration of doxorubicin.

SYMPTOMS AND TREATMENT OF OVERDOSAGE:

Acute overdosage of doxorubicin enhances the toxic effects of mucositis, leukopenia, and thrombolytopenia Treatment of acute overdosage consists of treatment of the severly myelosuppressed patients and granulocyte transfusion and sympomatic treatment of mucositis. Chronic overdosage with cumulative dosage exceeding 550 mg/m2 increase the risk of cardiomyopathy and result congestive heart failure. Treatment consist of vigorous management of congestive heart failure with digitals preparations and diuretics. The use of peripherals vasodilators has been recommend.

INCOPATIBILITIES:

Doxorubicin should not be mixed with 5-fluorouracil or heparin, Until specific compatibility data are available, it is recommended not to mix doxorubicin with other drugs.

CONTRAINDICATIONS:

Doxorubicin is contraindicated in patients with marked Myelosuppression induced by previous chemotherapy or Radiotherapy, in case of pre-existing heart diseases, or previous treatment with doxorubicin or any other anthracyclin with completion of cumulative dose.

STORAGE:

Store below 25°C. Protect from light.

PRESENTATION :

1) Zuvidox -10 Each single dose vial contains 10 mg of doxorubicin HCl, IP as a sterile red-orange lyophilized powder. Available as one individually cartoned vial.

2) Zuvidox -50 Each single-dose vial contains 50 mg of doxorubicin HCl, IP as a sterile red-orange lyophilized powder. Available as one individually cartoned vial.

Manufactured in India by:

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