EPIRUBICIN HYDROCHOLORIDE FOR INJECTION

ZEPIRUBIN Injection

Composition

Zepirubin 10

Each vial contains :

Epirubicin Hydrochloride BP 10 mg

Methyl Paraben IP 2 mg

Zepirubin 50

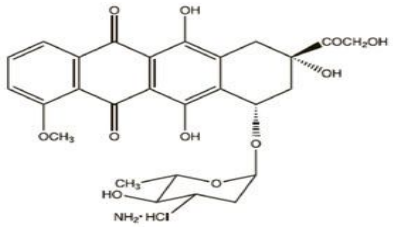
Each vial contains :

Epirubicin Hydrochloride BP 50 mg

Methyl Paraben IP 10 mg

DESCRIPTION

Epirbicin is an anthracycline cytotoxic agent and forma a complex with DNA by interacalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acid (DNA & RNA) and protein synthesis, Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity, Epirubicin also inhibits DNA helicase activity, preventing the enxymatic seperation of double - standard DNA & interfering with replication and transcription. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicaEpirbicin is an anthracycline cytotoxic agent and forma a complex with DNA by interacalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acid (DNA & RNA) and protein synthesis, Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity, Epirubicin also inhibits DNA helicase activity, preventing the enxymatic seperation of double - standard DNA & interfering with replication and transcription. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicals.



CLINICAL PHARMACOLOGY

In patients with normal hepatic and renal function, plasma levels after i.v. injection of 75-90 mg/m2 of the drug follow a tri-expontential decreasing pattern with a very fast first phase and a slow terminal phase

with a mean half-life of about 40 hours. Plasma levels of the drug's main metabolite, the 13-OH derivative, are constantly lower and virtually parallet to those of the liver, high plasma clearance values (0.91/min.) Indicate that this slow elimination is due to extensive tissue distribution. The drug does not cross the blood-brain barrier.

PHARMACOKENITCS

Epirubicin pharmacokinetics are linear over the dose range of 60-150 mg/m2,and plasma clearance is not affected by the duration of infusion or administration schedule, Pharmacokinetic parameters for epirubicin following 6-10 minutes, single dose]intravenous infusions of epirubicin at doses of 60-150 mg/m2 in patients with solid tumors are shown in TABLE 1. The plasma concentration declined in triphasic manner with mean halt-lives for the alpha, beta & gamma phases of about 3 minutes, 2.5 hrs and 33 hours respectively. Epirubicin pharmacokinetics are linear over the dose range of 60-150 mg/m2,and plasma clearance is not affected by the duration of infusion or administration schedule,

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TABLE : Summ of mean (+SD) Pharmacokinetic Parameters in
Patients with Solid Tumors Receiving intravenous Epirbicin 60 to 150mg/m2

Dose[2] (mg/m^2)	C^3_{max} (μg.mg)	AUC[4] (μg.h/mi)	$t^5_{1/2}$ (h)	CL[6] (L/h)	Vss[7] (L/kg)
60	5.7+1.6	1.6+0.2	35.3+9 ±	65+8 ±	21+2 ±
75	5.3+1.5	1.6+0.2	32.1+5 ±	83+14 ±	27+11±
120	9.0+3.5	3.4+0.7	33.7+4	65+13	23+7
150	9.3+2.9	4.2+0.8	31.1+6	69+13	21+7

1) Advanced solid tumors cancers, primarily of the lung.

2) N=6 Patients per dose level,

3) Plasma concentration at the end of 6-10 minute infusion.

4) Area under the plasma concentration curve.

5) Half life of terminal phase.

6) Plasma clearance.

7) Steady state volume of distribution.

INDICATIONS AND USAGE :

Epirubicin Hcl Injection is indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.

Renal Function

Serum creatinine should be assessed before and during therapy. Dosage adjustment is necessary in Patients with serum creatinine >5mg. / dL. See (a DOSAGE AND ADMINISTRATION). Patients undergoing Dialysis have not been studied.

Tumor-Lysis Syndrome As with other cytotoxic agents. Epirubicin HCI may induce hyperuicemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of highly chemosensitive neoplastic cells (tumors lysis syndrome). Other metabolic abnormalities may also occur. While not generally a problem in patients with breast cancer., physicians should consider the potential for tomor-lysis syndrome on potentially susceptible patients and should consider monitoring serum uric acid, potasssium, calcium, phosphate and creatining immediately after initial chemotherapy administration. Hydration, urine alkalinization and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

DOSAGE AND ADMINISTRATION

When Epirubicin is used as a single agent, the recommended dosage in adults in 60-90 mg/m2 body area : the drug should be indicated I.V. over 3-5 minutes and depending on the patients haematomadullar status, the dose should be repeated at 21 day intervals. Lower doses (60-75 mg/m2) are recommended for the patients whose bone marrow function has already been impaired by the previous chemotherapy or radio-therapy, by age, or neoplastic bone-marrow infiltration. The total dose per cycle may be divided over 2-3 successive days. When the drug is used in combination with other antitumor agents. the doses need to be adequately reduced. Since the major route of elimination of Epirubicin is the hepatobilary system, the dosage should be reduced in patients with impaired liver function, in order to avois an increase of overall toxicity. Moderate liver impairment (bilirubin : 1.4-3 mg/100 ml of BSP renton : 9-5%) requires a 50% reduction of dose while severe impairment (bikirubin>3mg/100 ml or BSP rention>15%) necessitates a dose reduction of in view of the limited amount of Epirubin excreted by this route.

DIRECTIONS FOR ADMINISTRATION

Epirubicin should be administered by intravenous injection. It is not active when given orally and should not be injection intramuscullarly or intrathecally. It is advisable to give the drug via the tubing of a freely running i.v. saline infusion after check that the needle is well placed in the vein. This method minimizes the risk of drug extravasation and makes sure that the vein is flushed with saline after the administration of the drug. Extravasaton of Epirubicin rapid dissolution from the vein during injection may given rise to severe tissue lesions, even necrosis. Venous sclerosis into the same vein. Epirubicin rapid dissolution should not be mixed with heparin due to chemical incompatibility which may lead to precipitation when the drug are in certain proportions. Epirubicin rapid dissolution can be used in combination with other antitumour agents, but is not recommended that it is mixed with these drugs in the same syringe.

PREPARATION KF INFUSION SOLUTION

Zepirubin 10 mg should be reconstituted to 5 ml by adding sterile water for injection I.P. and used before 24 hours after preparation. Zepirubin 50 mg should be reconstituted to 25 ml by adding sterile water for injection I.P. and use before 24 hours after preparation. Intravenous administration of Epirubicin HCI should ? be performed with caution. It is recommended that Epirubicin HCI be administered into the tubing of a freely flowing intravenos infusion (0.9% Sodium Chloride or 5% Glucose solution) over a period of 3-5 minutes. The technique is intended to minimize the risk of thrombosis or peruvians extravasation.

A direct push injection is not recommended due to the risk of return needle aspiration. Venous sclerosis may result from injection into small vessels or repeated injection into the same vein (see PRECAUTIONS). Beside above regimens. Several other protocols has been discussed in different published articles.

Warning

See also PRECAUTIONS, Carcinogenesis, Mutagenesis and impairment of Fertility and pregnancy Category D.Epirubicin HCI injection should be administered only under the supervision of qualified physicians experienced in the use of cytotoxic therapy. Before

beginning treatment with Epirubicin, patients should recover from acute toxicity (such as stoma titis, newtropenia thrombocytopenia and generalized infections) of prior cytotoxic treatment. Also, initial treatment with Eprirubicin HCI should be preceded by a careful baseline assessment of blood counts, serum levels of total bilirubin, AST and creatinine and cardiac function as measured by left ventricular ejection function (LVEF). Patients should be carefully monitored during treatment for possible clinical complications due to myelosuppression. Supportive care may be necessarily for the treatment of severe nuetropenia and severe infections complications. Monitoring for potential cardiotoxicity is also important, epecially with greater cumulative exposure to Epirubicin.

Severe local tissue necrosis will occur if there is extraveasation during administration.Epirubicin must not be given by the intramuscular or substances route. Myocardial toxicity, manifested in its either during therapy with Epirubicin or months to years after termination therapy. The probability of with Epirubicin or months to years after termination therapy. The probability of developing clinically evident CHF is estimated as approximately 0.9& at a cumulative dose of 550mg/m2, 1.6% at 700 mg/m2, and 3.3% at 90 mg/m2. In the adjuvant treatment if breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m2, The risk of developing CHF increases rapidly with increasing total cumulative dosed of Epirubicin in excess of 900 mg/m2,this cumulative dose should only be exceeded with extreme caution. Active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastial/pericardial area, previous therapy with other anthracyclines, or concomitant use of other anthracenediones, or concomitant use of other cardio toxic drugs may increase the risk of cardian toxicity. Cardiac toxicity with Epirubicin HCI may occur at lower cumulative doses whether or not cardiac risk factors are present. Secondary acute myelogenous leukemia (AML) has been reported in patients with breast cancer treated with anthracyclines, including Epirubicin. The occurrence of refractory secondary leukemia is more common when such drugs are given in combination with DNA damaging antineoplastic agents, when patients with impaired hepatic function, Severe myelosuppression may occur

Epirubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. Hematologic Toxicity A dose dependent, reversible leukopenia and / or neutropenia is the predominant manifestation of hematologic toxicity associated with Eprirubicin and represents the mist common acute dose - limiting toxicity of this drug. In most cases the WBC nadir is reached 10-14 days from drug administration. Leukopenia/neutropenia is usually transient, with WBC and neutrophil counts generally returning to normal values by day 21 after drug administration. As with other cytotoxic agents, Epirubicin HCI at the recommended dose in combination with cyclophosphamide and fluorouracil can produce severe leukopenia and neutropenia. Severe thrombocy- topenia and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, septicemia, septic shock, hemorrhage, tissu hypoxia, symptomatic anemia or death. If myelosuppressive complications occur, appropriate supportive measure (e.g. intravenous antibiotics, colony stimulating factors,

transfusions) may be required. Myelosuppression requires careful monitoring. Total and differential white blood cell (WBC), red blood cell and platelet counts should be assessed before and during each cycle of therapy with Epirubicin HCI.

Cardiac Function Cardiotoxicity is a known risk of anthracyclines treatment. Anthracyclines induced cardiac toxicity may be manifested by early (or acute) or late (delayed) events. Early cardiac toxicity of Epirubicin consists mainly of sinus tachycardia an / or ECG abnormalities such as nonspecific ST-T wave changes, but 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 considered an indication for the suspension of Epirubicin treatment. Delayed cardiac toxicity results from a characteristics cardiomyopathy that is manifested by reduced LVEF and / or signs and symptoms of congestive heart failure (CHF) such as tachycardia, yspnea, puirnonary edema, dependent edema, hepatomegaly, ascites, pleural effusion, gallop rhythm. Life theraening CHF is the most severe form of anthracycline induced cardiomyopathy, This toxicity appears to be dependent on the cumulative dose of Epirubicin HCI or within 2-3 months after ompletion of treatment but later events (several months to years after treatment termination) Cardiac Function Cardiotoxicity is a known risk of anthracyclines treatment. Anthracyclines induced cardiac toxicity may be manifested by early (or acute) or late (delayed) events. Early cardiac toxicity of Epirubicin consists mainly of sinus tachycardia an / or ECG abnormalities such as nonspecific ST-T wave changes, but 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 considered an indication for the suspension of Epirubicin treatment. Delayed cardiac toxicity results from a characteristics cardiomyopathy that is manifested by reduced LVEF and / or signs and symptoms of congestive heart failure (CHF) such as tachycardia, dyspnea, puirnonary edema, dependent edema, hepatomegaly, ascites, pleural effusion, gallop rhythm. Life theraening CHF is the most severe form of anthracycline induced cardiomyopathy, This toxicity appears to be dependent on the cumulative dose of Epirubicin HCI or within 2-3 months after completion of treatment but later events (several months to years after treatment termination) have been reported\Secondary Leukemia The occurrence of secondary acute myelogenous 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 pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been esclated.These leukemia can have a short 1-3 years latency period.

Liver Functon The major route of elimation of Epirubicin is the hepatobiliary system.serum total bilirun and AST levels should be evaluated before and during treatment with Epirubicin HCI. Patients with evaluated bilirubin or AST may experience slower clearance of drug with an increase in overalls toxocity. Lower doses are recommended in these patients (see DOSAGE AND ADMINISTRATION). Patients with severe hepatic impairment have not been evaluated; therefore Epirubicin should not be used in this patient population.

(about 0.1 times the maximum recommended single human dose on a body surface area basis) on days 10-12 of gestation induced abortion, but no other signs of embryo fetal toxicity or teratogenecity were observed . When dose up to 0.5 mg/kg/day Epirubicin were administered to rat darms from day 17 of gestation to day 21 after delivery (About 0.025 times the maximum recommended single human dose on

a body surface area basis)". no permanent changes were observed in the development, functional activity, behaviour, or reproductive performance of the offspring. There are no adequate and well - controlled studies in pregnant women controlled.

NURSING MOTHERS

Epiruicin was excreted into milk of rats. It is not know whether Epirubicin is excreted in human milk. Because many drugs. including other anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Epirubicin, mothers should discontinue nursing prior to taking this drug.

PRECAUTIONS

General

Epirubicin HCI injection is administered by intravenous infusion. Venous sclerosis may result from an injection in to a small vessel or from repeated injections in to the same vein. Extravasation of Epirubicin during the infusion may cause local pain, severe tissue lesions and necrosis. It is recommended that Epirubicin HCI be slowly administered in to the tubing of a freely running intravenous infusion. If possible, veins over joints or in extremities with compromised venous orlymphatic drainage should be avoided. The dose should be administered over 3-5 minutes. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Penvenous infiltration may occur without causing pain. Facial flushing as well as local erythemaous streaking along the vein, may be indicative of excessevely rapid administration. It may precede local phlebits or thrombo phelbitis. Patients administered the 120 mg/m2 regimen of Epirubicin Hcl as a component of combination chemotherapy should also receive prophylactic antibiotic with trimethoprim sulfamethaxazole.

LABORATORY TESTS

Blood counts, including absolute neutrophill counts and liver function should be assessed before and during each cycle of therapy with Epirubicin.Repeated evaluations of LVEF Should be performed during therapy. See WARNINGS Drug /Laboratory test interactions There are known interactions between Epirubicin HCI and Laboratory tests.

Carcinogenesis, Mutagenesis and Impairment of Fertility Treatment related acute myelogenous leukemia has been reported in women treated with Epirubicin based adjuvant chemotherapy regimens (see WARNINGS Secondary leukemia). Conventiona lalong term animal studies to evaluate the carcinogenic potential data are not available. Epirubicin HCI could induce chromosomal damage in human spernatozoa due to its genotoxic potential Men undergoing treatment with Epirubicin HCI should use effective

Contraceptive methods. Epirubicin HCI may cause irreversible amenorrhea (Premature menopause) in premenopausal women. Pregnancy category D Epirubicin HCI may cause fetal Harm When administered to a pregnant woman. Administration of 0.8 mg/kg/day intravenously of Epirubicin to rats (About 0.04 times the maximum recommended single human ?dose on a body surface area basis) during days 5-15 of gestation was embryotoxic (increased resorption and post implantation loss) and caused fetal harm when administered to a pregnant woman. Administration 2 mg/kg/day intravenously of Epirubicin to rats (about 0.1 times the maximum recommended single human dose on body surface area basis) on days 9 and 10

of gestation was embryotoxic (increase late resorptions post implanations lossed and dead fetuses and decreased live fetuses), retarded fetal growth (decreased body weight) and caused decreased placental weight, This dose was also teratogenic, causing numerous external (anal tresia, misshapen tall, abnormal genital tubercle) visceral (primarily gastrointestinal, urinary and cardiovascular systems) and skeletal (deformed) long bones and gridles, rib abnormalities, irregular spinal ossification) malformations.Administration of intravenous Epirubicin to rabbits at dose up to 0.2 mg/kg/day (about 0.02 times the maximum recommended single human dose on a body surface area basis) during days 6 to 18 of gestation was not embryotoxic, but meternally toxic dose of 0.32 mg/kg day increased abortion and delayed ossification. Administration of a meternally toxic intravenous dose of 1 mg / kg/day Epirubicin to rabbits

ADVERSE REACTIONS

Apart from myelosuppression and cardiotoxicity (descriped under precautions the following adverse reactions have been described)

Alopecia, normally reversible, appears in 60-90% of treated and cases it is accompained by the lack of beard growth in males:

Mucositis may appear 5-10 days after the start of treatment and usually involves stoma titis with areas of painful erosions, mainly along the sides of the tongue on the sublingual mucosa;

Gastro-intestinal disturbances, such as nausea, vomiting and diarrhoea; Hyperpyrexia.

Drug Interactions

Epirubicin Hydrochloride for Injection when used in combination with other cytotoxic drugs may show on-treatment additive toxicity, especially hematologic and gastrointestinal effects. Concomitant use of Epirubicin Hydrochloride for Injection with other cardioactive compounds that could cause heart failure (e.g., calcium channel blockers), requires close monitoring of cardiac function throughout treatment. There are few data regarding the coadministration of radiation therapy and epirubicin. In adjuvant trials of epirubicin-containing CEF-120 or FEC-100 chemotherapies, breast irradiation was delayed until after chemotherapy was completed. This practice resulted in no apparent increase in local breast cancer recurrence relative to published accounts in the literature. A small number of patients received epirubicin-based chemotherapy concomitantly with radiation therapy but had chemotherapy interrupted in order to avoid potential overlapping toxicities. It is likely that use of epirubicin with radiotherapy may sensitize tissues to the cytotoxic actions of irradiation. Administration of Epirubicin Hydrochloride for Injection after previous radiation therapy may induce an inflammatory recall reaction at the site of the irradiation. Epirubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicin metabolism, pharmacokinetics, therapeutic efficacy, and/or toxicity. Cimetidine increased the AUC of epirubicin by 50%. Cimetidine treatment should be stopped during treatment with Epirubicin Hydrochloride for Injection.

OVERDOSAGE

The observed adverse events due to over dosage were qualitatively similar to known toxicities of Epirubicin. Most of the patients recovered with appropriate supportive care. If an over dosage occurs, supportive treatment (including antibiotic therapy, blood and platelet transfusions, colony stimulating factors and intensive care as needed) should be provided until the recover of toxocities. ? Delayed CHF

has been observed months after anthracycline. Patients must be observed carefully over time for signs of CHF and provided with appropriate supportive therapy.

CONTRANDICATIONS

Patients should not be treated with Epirubicin HCL Injection if they have any of the following conditions Baseline neutrophil cound < 1500 cells/mm2, severe arhythmia, previous treatment with anthracyclines up to the maximum cumulative dose : hypersensitivity to epirubicin, other anthracyclines, or antharacenediones : of sever hepatic.

STORAGE : Store between 15 C and 30 C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

PRESENTATION

Zepirubin 10 mg.....Epirubicin HCI 10 mg vial

Zepirubin 50 mg.....Epirubicin HCI 50 mg vial

Zepirubin 100mg ..... Epirubicin HCl 100mg vial

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
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Link Road, Ghatkopar (East), Mumbai 400075.
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