Injection

E-RUBICIN

Epirubicin HCl
50 mg, 10 mg
Antineoplastic / Cytotoxic

Action and clinical pharmacology: The mechanism of action of epirubicin, although not completely elucidated, is mainly related to its ability to bind to nucleic acids by intercalation of the planar anthracycline nucleus with the DNA double helix. Binding to cell membranes as well as to plasma proteins may also be involved. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity, mutagenesis and chromosomal aberrations. Animal studies have shown activity in a wide spectrum of experimental tumors, immunosuppression, mutagenic and carcinogenic properties in rodents, and a variety of toxic effects, including myelosuppression in all species and atrophy of the seminiferous tubules of testes in rats and dogs. Data from different animal species and in vitro models have shown that epirubicin is less toxic, and in particular less cardiotoxic than doxorubicin. At equally effective doses, epirubicin produces less severe nonhematologic side effects such as vomiting and mucositis,
than doxorubicin.

Pharmacokinetics: Pharmacokinetic studies show an initial rapid elimination of the parent compound from plasma. The terminal half-life of elimination of the parent drug from plasma approximates 30 to 40 hours in man. Urinary excretion accounts for approximately 9 to 10% of the administered dose in 48 hours. Biliary excretion represents the major route of elimination, about 40% of the administered dose being recovered in the bile in 72 hours. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol. The 4'-0-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel to those of the unchanged drug. Impairment of hepatic function results in higher plasma levels. Distribution studies in the rat have shown that epirubicin does not appear to cross the blood-brain barrier.

Indications And Clinical Uses: Epirubicin has been used successfully as a single agent and also in combination with other chemotherapeutic agents to produce regression in a variety of tumor types such as lymphoma, lung, cancer of the breast, ovary and stomach. It is recommended for the treatment of metastatic breast cancer, small cell lung cancer (both limited and extensive disease), advanced non-small cell lung cancer, non-Hodgkin's lymphoma, Hodgkin's disease, Stage III and IV (FIGO) ovarian carcinoma and metastatic and locally unresectable gastric carcinoma. In clinical studies epirubicin has been safely used in combination with fluorouracil and cyclophosphamide, when considered appropriate by the physician, in the adjuvant treatment of early stage breast cancer (Stage II to III A). Several other solid tumors have shown responsiveness to epirubicin but data are not yet sufficient to justify specific recommendations.

Contra-Indications: Therapy should not be started in patients who have marked myelosuppression induced by prior treatment with other antitumor agents or by radiotherapy. Therapy should not be initiated in patients with a history of severe cardiac disease. Preliminary data suggest that in such cases cardiac toxicity may occur at doses lower than the recommended cumulative limit. Epirubicin treatment is generally contraindicated in patients who have received prior treatment with maximum recommended cumulative doses of doxorubicin, daunorubicin, mitoxantrone or mitomycin C.

Manufacturers' Warnings in clinical states: Caution: Epirubicin is a potent drug and should be used only by physicians experienced with cancer chemotherapeutic drugs (see Precautions). Blood counts and hepatic function tests should be performed regularly. Irreversible cardiac toxicity may occur as the cumulative dose approaches 1 000 mg/m Cardiac monitoring is advised in those patients who have received mediastinal radiotherapy, other anthracycline or anthracene therapy, with pre-existing cardiac disease, or received prior epirubicin cumulative doses exceeding 650 mg/m. Serious irreversible myocardial toxicity with resultant congestive heart failure and/or cardiomyopathy may be encountered as the cumulative dose approaches 1 000 mg/m This toxicity may occur at lower cumulative doses in patients who have received prior anthracycline, mitomycin C or anthracene therapy and/or mediastinal radiotherapy and in those with a history or presence of cardiac disease. Although uncommon, left ventricular failure may occur, particularly in patients who have received a cumulative dose that exceeds 1 000 mg/m or a lower cumulative dose in patients who have received radiotherapy to the mediastinal area. The total dose administered to a patient should also take into account prior or concomitant therapy with related anthracyclines and anthracenes. Congestive heart failure and/or cardiomyopathy may be encountered several weeks after discontinuation of therapy. Available evidence appears to indicate that cardiotoxicity is cumulative across members of the anthracycline and anthracene class of drugs. Patients who have previously received other anthracyclines or anthracenes are at particular risk for possible cardiotoxic effects of epirubicin at a lower total dose than previously untreated patients and, therefore, should be carefully monitored. Anthracycline-induced cardiac failure is often resistant to currently available therapeutic and physical measures used for the treatment of cardiac failure. Early clinical diagnosis of drug-induced heart failure is essential. Treatment measures include digitalis, diuretics, peripheral vasodilators, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent ECG changes. An ECG, echocardiogram or radionuclide angiography (MUGA) performed at baseline and prior to each dose or course after a cumulative dose of 650 mg/mof epirubicin is suggested. Transient ECG changes consisting of T-wave flattening, S-T depression and arrhythmias occurring up to 2 weeks after a dose or course of epirubicin are presently not considered indications for suspension of epirubicin therapy. Epirubicin cardiomyopathy has been reported to be associated with a reduction of the ejection fraction as determined by radionuclide scan or echocardiography. None of these tests have yet consistently identified those individual patients that are approaching their maximally tolerated cumulative dose of epirubicin. If test results indicate a change in cardiac status associated with epirubicin therapy, the benefit of continued therapy must be carefully weighed against the risk of producing irreversible cardiac damage. Careful hematologic monitoring is required since bone marrow depression, primarily of leukocytes may occur. With the recommended dosage schedule (see Dosage) leukopenia is transient, reaching its nadir 10 to 14 days after treatment, with recovery usually occurring by the 21st day. White blood cell counts as low as 1 000/mm are to be expected during treatment. Red blood cell and platelet levels should be monitored since they may also be suppressed. Hematologic toxicity may require dose reduction or delay or suspension of therapy. Persistent myelosuppression may result in infection or hemorrhage. Epirubicin may potentiate the toxicity of other anticancer therapies as well as radiation-induced toxicity to the myocardium, mucosa and skin. Toxicity to recommended doses of epirubicin is enhanced by hepatic impairment. Therefore, prior to dosing, an evaluation of hepatic function, using conventional clinical laboratory tests such as AST, ALT, alkaline phosphatase and bilirubin determinations is recommended (see Dosage). Epirubicin must not be administered by i.m. or s.c. injection. Severe local tissue necrosis can occur if epirubicin is extravasated during i.v. administration. Extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle (see Dosage). If signs or symptoms of extravasation occur, the injection or infusion should be terminated immediately and restarted in another vein. Epirubicin and related compounds have also been shown to have mutagenic and carcinogenic properties when tested in experimental models. Epirubicin imparts a red coloration to the urine for 1 to 2 days after administration. Patients should be advised to expect this during active therapy.

Pregnancy: There is no conclusive information about epirubicin adversely affecting human fertility, or causing teratogenesis; however, at high doses epirubicin is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. Therefore women of childbearing potential should be advised to avoid pregnancy. If epirubicin is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be informed of the potential hazard to the fetus.

Lactation: Mothers should be advised not to breast-feed while undergoing chemotherapy with epirubicin.

Precautions: Initial treatment requires close observation of the patient and extensive laboratory monitoring. As with other cytotoxic drugs, epirubicin may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The physician should monitor the patient's serum chemistry, blood uric acid levels and be prepared to institute appropriate measures that might be necessary to control this problem. Epirubicin is not an antimicrobial agent.

Adverse reactions: Dose limiting toxicities are myelosuppression and cardiotoxicity (see Warnings). Other reactions reported are: Cutaneous: Reversible partial or complete alopecia occurs in most patients. Alopecia and lack of beard growth in males are usually reversible. Recall of skin reaction associated with prior radiotherapy may occur.

Gastrointestinal: Acute nausea and vomiting occur frequently in most patients. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) has been reported to occur 5 to 10 days after administration. This may lead to ulceration and represents a site of origin for severe infections. Diarrhea has been reported.

Local: Severe cellulitis, vesication, local pain and tissue necrosis can occur if epirubicin is extravasated during administration (see Dosage). Erythematous streaking and/or transient urticaria along the vein proximal to the site of administration may occur. Venous sclerosis may result from injection into small veins or repeated injection into the same vein.

Hematological: The occurrence of secondary acute myeloid leukemia with or without a preleukemic phase has been reported rarely in patients concurrently treated with doxorubicin in association with DNA-damaging antineoplastic agents. Such cases could have a short (1 to 3 years) latency period.
Other: Phlebitis, fever, and malaise have been reported following administration.

Symptoms and treatment of overdose: Symptoms and Treatment: Acute overdosage may cause an acute myocardial dysfunction within 24 hours. Pronounced mucositis, leukopenia and thrombocytopenia could be observed within 7 to 14 days. Treatment of acute overdosage consists of hospitalization of the severely myelosuppressed patient, platelet and granulocyte transfusions, antibiotics and symptomatic treatment of mucositis.

Dosage and administration: See Guidelines for Safe Preparation and Handling. A variety of dose schedules have been used. The following recommendations are for use as a single agent or in combination with other chemotherapeutic agents. Dosage is usually calculated on the basis of body surface area. The lower dose should be given to patients with inadequate marrow reserves due
to old age, or prior therapy, or neoplastic marrow infiltration.

Carcinoma of the Breast: Single Agent: The most commonly used dosage schedule in metastatic breast cancer when employed as a single agent for adults is 75 to 90 mg/madministered at 21-day intervals. The recommended single dose may be divided over 2 successive days. An alternative schedule of weekly doses of 12.5 to 25 mg/mhas been used and has been reported to produce less clinical toxicity than higher doses given every 3 weeks.

Combination Therapy: In metastatic breast cancer epirubicin can be used in combination with cyclophosphamide and 5-fluorouracil (Fec), at a dose of 50 mg/m. Clinical studies have shown that epirubicin 50 to 60 mg/mgiven on Days 1 and 8 every 4 weeks in combination with fluorouracil and cyclophosphamide, when considered appropriate by the physician, can be used safely in the adjuvant treatment of early stage breast cancer (Stage II to IIIA).

Small Cell Lung Cancer: Single Agent: Epirubicin, as a single agent, can be used at 90 to 120 mg/m administered every 3 weeks.

Combination Therapy: Epirubicin has been used in several different combinations with other antineoplastic agents at doses ranging from 50 to 90 mg/m The following combinations have proven effective: epirubicin in combination with either cisplatin or ifosfamide; epirubicin with cyclophosphamide and vincristine (CEV); epirubicin with cyclophosphamide and etoposide (CEVP-16) and epirubicin with cisplatin and etoposide.

Non small Cell Lung Cancer: Single Agent: Epirubicin, as a single agent, can be used at doses of 120 to 150 mg/m administered day 1, every 3 to 4 weeks.

Combination Therapy: Epirubicin, in combination with etoposide, cisplatinum, mitomycin, vindesine and vinblastine, can be used at doses of 90 to 120 mg/m administered day 1, every 3 to 4 weeks.

NonHodgkin's Lymphoma: Single Agent: Epirubicin, as a single agent, can be used at doses of 75 to 90 mg/m at 21-day intervals.

Combination Therapy: Epirubicin at doses of 60 to 75 mg/mcan be used in combination with cyclophosphamide, vincristine and prednisone with or without bleomycin (replacing doxorubicin in the CHOP, CHOP-Bleo or BACOP regimens) for the treatment of newly diagnosed non-Hodgkin's lymphoma. **Hodgkin's Disease: Combination Therapy:** Epirubicin, in combination with bleomycin, vinblastine and dacarbazine, can be used at 35 mg/mevery 2 weeks or 70 mg/mevery 3 to 4 weeks (replacing doxorubicin in the ABVD regimen).

Ovarian Cancer: Single Agent: In patients with prior therapy, epirubicin can be used as a single agent at doses of 50 to 90 mg/m at 3- to 4-week intervals.

Combination Therapy: In patients with prior therapy, epirubicin can be used in combination at doses of 50 to 90 mg/m at 3 to 4 week intervals. Epirubicin at doses of 50 to 90 mg/m in combination with cisplatin and cyclophosphamide can be used for initial therapy of ovarian cancer repeated at 3 to 4 week intervals.

Gastric Cancer: Single Agent: Epirubicin, as a single agent can be used for the treatment of locally unresectable or metastatic gastric carcinoma, at doses of 75 to 100 mg/m

Combination Therapy: Epirubicin at a dose of 80 mg/m can be used in combination with fluorouracil for the treatment of locally unresectable or metastatic gastric carcinoma. As epirubicin is excreted primarily by the biliary system, its dosage must be reduced in patients with impaired liver function indicated by elevated bilirubin values as follows: Serum bilirubin 1.2 to 3 mg/dL give 1/2 normal dose;>3 mg/dL give 1/4 normal dose. Renal impairment does not appear to call for dose reduction in view of the limited amount of epirubicin excreted by this route. Care in the administration of epirubicin will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On i.v. administration extravasation may occur with or without an accompanying stinging or burning 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 it is known or suspected that s.c. extravasation has occurred, the following steps are recommended: attempt aspiration of the infiltrated epirubicin solution; local intermittent application of ice for up to 3 days; elevation of the affected limb; close observation of the lesion; consultation with a plastic surgeon familiar with drug extravasation if local pain persists or skin changes progress after 3 to 4 days. If ulceration begins, early wide excision of the involved area should be considered.

Preparation of Solution: Skin reactions may occur. Caution in handling of the powder and preparation of the solution must be exercised. The use of gloves, eye protection, masks and protective clothing is recommended. If epirubicin powder or solution contacts the skin or mucosa, immediately wash thoroughly with soap and water. If it is spilled into the conjunctiva immediately flush with saline or water.

Epirubicin 50mg vials should be reconstituted with 25mL of sterile water for injection to give a final concentration of 2 mg/mL of epirubicin HCl. Epirubicin 10mg vials should be reconstituted with 5mL of sterile water for injection to give a final concentration of 2 mg/mL of epirubicin HCl. Bacteriostatic diluents are not recommended.

After adding the diluent, the vial should be shaken until the contents are dissolved. A slight suspension may form which will completely dissolve on further shaking. The solution should be protected from exposure to direct light and any unused solution should be discarded.

Availability and storage:
E-RUBICIN - 50 INJECTION: Each vial of sterile, red-orange powder contains: Epirubicin HCl 50 mg.
E-RUBICIN - 10 INJECTION: Each vial of sterile, red-orange powder contains: Epirubicin HCl 10 mg.

Do not store above 25°C.
To be used under medical supervision
Keep out of the reach of children.

ای۔روبیسن انجکشن

ایپی روبیسن ہائیڈروکلورائیڈ

10 ملی گرام، 50 ملی گرام

دوا کو ۲۵ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

مستند ڈاکٹر کی نگرانی میں استعمال کریں۔

بچوں کی پہنچ سے دور رکھیں۔

Revised. June.2016

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