30 mm

30 mm

50 mm

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

EPICN

(Epirubicin Hydrochloride Injection 2 mg/ml)

Name and strength of active ingredient
Epirubicin Hydrochloride 2 mg/ml

Therapeutic Code
Antineoplastic and Immunomodulating Agent
ATC code: L01DB03

Dosage form
Injection

Product Description
A clear red solution filled in clear glass vial. When examined under suitable conditions of visibility it should be practically free from particles.

Pharmacodynamics & Pharmacokinetics
Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agent. ATC code: L01D B03.
The mechanism of action of epirubicin is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin has proved to be active on a wide spectrum of experimental tumors including L1210 and P388 leukaemias, sarcomas SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumors transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

Pharmacokinetic properties
In patients with normal hepatic and renal function, plasma levels after intravenous injection of 60-150 mg/m^2 of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol. The 4'-O-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 those of the unchanged drug.

Epirubicin is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution. Urinary excretion accounts for approximately 9-10% 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 drug does not cross the blood brain barrier.

Indication/Usage
Epirubicin has produced responses in a wide spectrum of neoplastic diseases, and is indicated for the treatment of:
- breast cancer;
- gastric cancer;
- ovarian cancer;
- small cell lung cancer;
- lymphoma (non-Hodgkin's lymphoma);
- advanced/metastatic soft tissue sarcoma;
- superficial bladder cancer (Tis; Ta)

In bladder cancer, Epirubicin is also indicated in the Prophylaxis of reccurence after transurethral resection of stage T1 papillary cancers and stage Ta Multifocal papillary cancers (Grade 2 and 3).

Recommended Dose
Epirubicin is for intravenous or intravesical use only.
Epirubicin is a cytotoxic drug that is usually administered to cancer patients by intravenous injection. However, intravesical administration has been found beneficial in the treatment of superficial bladder cancer as well as in the prophylaxis of tumour recurrence after transurethral resection. Epirubicin has been also used by the intra-arterial route in the attempt to produce intense local activity with reduced general toxicity. Since this technique is potentially hazardous and can lead to widespread necrosis of the perfused tissue, intra-arterial administration should only be attempted by those physicians with this technique.

Intravenous (IV) Administration
Dosage is usually calculated on the basis of body surface area (mg/m^2). The total epirubicin dose per cycle to be delivered may differ according to its use within a specific treatment regimen (eg. given as a single agent or in combination with other cytotoxic drugs) and according to the therapeutic indication (eg. in the treatment of breast and lung cancer epirubicin is also used at doses higher than conventional).

Intravenous administration of epirubicin should be performed with caution. It is recommended to administer epirubicin into the tubing of a freely flowing IV infusion (isotonic sodium chloride or 5% glucose solution) over a period of 3 to 5 minutes. This technique is intended to minimize the risk of thrombosis or perivenous extravasation which could lead to severe cellulitis, vesication and tissue necrosis. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Conventional dose
When epirubicin is used as a single agent, the recommended dose per cycle in adults is 60-90mg/m^2 of body surface area. The total dose per cycle may be given as a single dose or divided over 2-3 successive days. Under conditions of normal recovery from drug-induced toxicity (particularly bone marrow depression and stomatitis), each treatment cycle could be repeated every three weeks.

High dose
Lung cancer
Epirubicin as a single agent for the high dose treatment of lung cancer should be administered according to the following regimens.
Small cell lung cancer (previously untreated)
120mg/m^2 day 1, every three weeks.
Non-small cell lung cancer (squamous large cell and adenocarcinoma, previously untreated)
135mg/m^2 day 1 or 45mg/m^2 days 1, 2, 3, every three weeks.

Breast cancer
Doses up to 1 35mg/m^2 as single agent and 120mg/m^2 in combination, every 3-4 weeks proved to be effective and well tolerated of breast cancer.

In the adjuvant treatment of early breast cancer patients with positive lymph nodes, doses ranging from 100mg/m^2 to 120mg/m^2 every 3-4 weeks are recommended. Lower doses (60-75mg/m^2 for conventional dose schedules or105-120 mg/m^2 for high dose schedules) or a longer interval between cycles are recommended for heavily pretreated patients, elderly patients, or in the presence of neoplastic bone marrow infiltration. If epirubicin is used in combination with other cytotoxic drugs with potentially overlapping toxicities, the recommended dose per cycle should be reduced accordingly.

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted through this route. However, since the major route of elimination of epirubicin is the hepatobiliary system, the dosage has to be reduced in patients with impaired liver function in order to avoid an increase of overall toxicity.

Intravesical Administration
For the treatment of superficial bladder tumors, a therapy of 8 weekly instillations of 50mg (in 25-50ml of saline solution) is recommended. In the case of local toxicity (chemical cystitis), a dose reduction to 30mg is advised. For carcinoma in-situ, depending on the individual tolerability of the patient, the dose may be increased up to 80mg. For prophylaxis of recurrences after transurethral resection of superficial tumors, 4 weekly administrations of 50mg followed by 11 monthly instillations at the same dosage are recommended. Generally, the instillate should be retained in the bladder for one hour and during instillation the pelvis of the patient should be rotated to ensure the most extensive contact of the solution with the vesical mucosa. To avoid undue dilution with the urine, the patient should be instructed not to drink any fluid in the twelve hours prior to instillation.

Route of Administration
Epirubicin is for intravenous or intravesical use only.

Contraindication
Epirubicin is contraindicated in:
- Patients who have demonstrated hypersensitivity to the active substance or to any of the excipients.
- Patients with marked myelosuppression induced by previous treatment with either other anti-neoplastic agents or radiotherapy.
- Patients treated with maximal cumulative doses of other anthracyclines such as doxorubicin or daunorubicin.
- Patients with current or previous history of cardiac impairment.

Warnings & Precaution
Epirubicin should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of epirubicin.

Extravasation of epirubicin from the vein during injection may cause severe tissue lesions and necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Careful baseline monitoring of various laboratory parameters and cardiac function should precede initial treatment with epirubicin.

During treatment with epirubicin, red blood cell, white blood cell, neutrophil and platelet counts should be carefully monitored both before and during each cycle of therapy. Leucopenia and neutropenia are usually transient with conventional and high-dose schedules, reaching a nadir between the 10th and 14th day, values should return to normal by the 21st day; they are more severe with high dose schedules.

Thrombocytopenia (< 100,000 platelets/mm^3) is experienced in very few patients, even following high doses of epirubicin.

In establishing the maximal cumulative dose of epirubicin, consideration should be given to any concomitant therapy with potentially cardiotoxic drugs. A cumulative dose of 900-1000 mg/m^2 should only be exceeded with extreme caution with both conventional and high doses of epirubicin. Above this level the risk of irreversible congestive heart failure increases greatly. An ECG is recommended before and after each treatment cycle. Alterations in the ECG tracing, such as flattening or inversion of the T-wave, depression of the S-T segment, or the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment. With cumulative doses <900 mg/m^2 , there is evidence that cardiac toxicity rarely occurs. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart failure of the type described for other anthracyclines. Cardiomyopathy induced by anthracyclines is associated with persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the ejection fraction. Cardiac monitoring of patients receiving epirubicin treatment is highly important and it is advisable to assess cardi c function by non-invasive techniques such as ECG, echocardiography and, if necessary, measurement of ejection fraction by radionuclide angiography.

Heart failure may appear several weeks after discontinuing therapy with epirubicin and may be unresponsive to specific medical treatment. The potential risk of cardiotoxicity may increase in patients who have received concomitant, or prior, radiotherapy to the mediastinal pericardial area.

(Front Side)

File Name : 6018107 -Epirubicin 2 mg per ml (Acc-Mal) 1X1V PIL
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Before commencing therapy with epirubicin, and if possible during treatment, liver function should be evaluated (SGOT, SGT, alkaline phosphatase, bilirubin). As with other cytotoxic agents, epirubicin may induce hyperuricaemia as a result of rapid lysis of neoplastic cells. Blood uric acid levels should therefore be checked so that this phenomenon may be recognised and properly managed. Epirubicin may impart a red colour to the urine for one or two days after administration.

Interaction with other medicaments
Heart failure has been reported even several weeks to several months after discontinuing treatment and the risk may be higher in patients with concomitant treatment with other potentially cardiotoxic agents such as high dose, cyclophosphamide or 5-fluorouracil. In such patients a reduction of the total cumulative dose may required.

Propranolol: concurrent administration of Epirubicin Hydrochloride Injection 2 mg/ml and propranolol may result in an additive cardiotoxic effect

Concurrent mediastinal radiotheraphy and Epirubicin Hydrochloride Injection 2 mg/ml may be associate with enhanced myocardial toxicity of Epirubicin Hydrochloride Injection 2 mg/ml. Epirubicin Hydrochloride Injection 2 mg/ml can be used in combination with other antitumour agents; but it is not recommended that is be mixed with these drugs in the same container.

Heparin: Epirubicin Hydrochloride Injection 2 mg/ml should not be mixed with heparin as these drugs are incompatible. Until specific compatibility data are available, it is not recommended that Epirubicin Hydrochloride Injection 2 mg/ml be mixed with other drugs.

Pregnancy and Lactation
There is no conclusive information as to whether epirubicin may adversely affect human fertility or cause teratogenesis. Experimental data, however, suggest that epirubicin may harm the foetus. Like most other anti-cancer agents, epirubicin has shown mutagenic and carcinogenic properties in animals. Both men and women receiving epirubicin should be informed of the potential risk of adverse effects on reproduction. Women of childbearing potential should be fully informed of the potential hazard to the foetus should they become pregnant during epirubicin therapy. In cancer chemotherapy, epirubicin should not be used in pregnant women or women of childbearing potential who might become pregnant unless the potential benefits to the mother outweigh the possible risks to the foetus. Epirubicin should not normally be administered to patients who are breast-feeding.

Side effects/Adverse Reactions
Blood and the lymphatic system disorders: Myelosuppression. The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase, has been reported rarely in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents. These leukaemias have a short (1-3 years) latency.

High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumors and has caused adverse events which are no different from those seen at conventional doses with the exception of reversible severe neutropenia (< 500 neutrophils/mm^3 for < 7 days) which occurred in the majority of patients. Only few patients required hospitalisation and supportive therapy for severe infectious complications at high doses. Cardiac disorders: Cardiotoxicity

Gastrointestinal disorders: Mucositis may appear 5-10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, mainly along the side of the tongue and the sublingual mucosa. Nausea, vomiting and diarrhoea have also been reported. Skin and subcutaneous tissue disorders: Alopecia, normally, reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males. Renal and urinary disorders: During intravesical administration, as drug absorption is minimal, systemic side effects are rare, more frequently chemical cystitis, sometimes haemorrhagic, has been observed. General disorders: Anaphylaxis and hyperpyrexia may occur. Fever, chills and urticarias have been reported rarely.

Signs & Symptoms of overdose and Treatment
Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 days. Treatment should aim to support the patient during this period and should utilise such measures as blood transfusion and reverse barrier nursing. Delayed cardiac failure has been seen with the anthracyclines up to 6 months after the overdose. Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines.

Incompatibilities
Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug, which includes sodium bicarbonate containing solutions. Only the diluents (Glucose 5% or Sodium Chloride 0.9%) should be used.

Neither the injection nor any diluted solution should be mixed with any other drugs. (A physical incompatibility with heparin has been reported).
Epirubicin should not be mixed with other drugs.

Storage
Store at 2°C to 8°C. Do not freeze.
Keep the Container in the outer in oldar to protect from light.

Shelf life
24 months

Package
EPICN (Epirubicin Hydrochloride Injection 2 mg/ml) is available in 5 ml, 10 ml, 25 ml and 100 ml vials.
5 ml in 5 ml Type-I clear tubular glass vial
10 ml in 10ml Type-I clear tubular glass vial
25 ml in 30 ml Type-I clear tubular glass vial
100 ml in 100 ml Type-I clear molded glass vial
Each Carton contains 1 glass vial.

Manufactured by:
INTAS PHARMACEUTICALS LTD.
Matoda-382 210, Dist. : Ahmedabad, INDIA

Product Registration Holder:
accord
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