

DATA SHEET

EPICCORD

Epirubicin hydrochloride

Presentation

10 mg/5 mL - The vial contains 10 mg of epirubicin hydrochloride, sodium chloride 45 mg, hydrochloric acid q.s. and water for injections q.s. to 5 mL (2 mg/mL).

20 mg/10 mL - The vial contains 20 mg of epirubicin hydrochloride, sodium chloride 90 mg, hydrochloric acid q.s. and water for injections q.s. to 10 mL (2 mg/mL).

50 mg/25 mL - The vial contains 50 mg of epirubicin hydrochloride, sodium chloride 225 mg, hydrochloric acid q.s. and water for injections q.s. to 25 mL (2 mg/mL).

200 mg/100 mL - The vial contains 200 mg of epirubicin hydrochloride, sodium chloride 900 mg, hydrochloric acid q.s. and water for injections q.s. to 100 mL (2 mg/mL).

Uses

Actions

Although it is known that anthracyclines can interfere with a number of biochemical and biological functions within eukaryotic cells, the precise mechanisms of epirubicin's cytotoxic and/or antiproliferative properties have not been completely elucidated. Cell culture studies have shown rapid cell penetration, with drug localisation mainly in the nucleus. At the molecular level, epirubicin can form a complex with the DNA by intercalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acids (DNA and RNA) and protein synthesis. In addition, such intercalation can trigger DNA cleavage by topoisomerase-II, yielding serious disturbances in the tertiary structure of DNA. As observed for doxorubicin, epirubicin can also be involved in oxidation/reduction reactions with generation of highly reactive and highly toxic free radicals. The antiproliferative and cytotoxic activity of doxorubicin may result from any of the mentioned mechanisms, and there may be others. Epirubicin has proved to be active against a wide spectrum of experimental tumours including L 1210 and P 388 leukaemias, SA 180 sarcoma (solid and ascitic forms), B 16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

Pharmacokinetics

Absorption: Epirubicin is not absorbed from the gastrointestinal tract. Since the drug is extremely irritating to tissues, it has to be administered by the intravenous route. Intravesical administration has been demonstrated to be feasible; following this route of administration, passage of epirubicin into the systemic circulation is minimal.

Distribution: Following IV administration, epirubicin is quickly and widely distributed into the extravascular compartments, as indicated by a very fast distribution half-life and a steady-state distribution volume in excess of 40 L/kg. In spite of its wide distribution volume, however, epirubicin does not cross the blood-brain barrier in detectable amounts.

Metabolism: Epirubicin is metabolised to a significant extent, mainly by the liver. The major metabolites that have been identified are epirubicinol (13-OH epirubicin), which possesses a certain degree of antitumour activity, and glucuronides of epirubicin and epirubicinol. Plasma levels of the main metabolite, epirubicinol, are lower than those of the unchanged drug. From the metabolic viewpoint, the 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for its reduced toxicity.

Excretion: In patients with normal hepatic and renal function, epirubicin plasma levels after IV administration of 60-150 mg/m² follow a tri-exponential decreasing pattern, with a slow terminal phase (t_{1/2}) of 30 to 40 hours. These doses are within the limits of pharmacokinetic linearity. The terminal half-life of epirubicinol is similar to that of epirubicin. Plasma clearance is in the range of 0.9 to 1.4 L/min. Epirubicin is eliminated mainly through the liver: about 38% of the administered dosage is recovered in 24 hour bile in the form of epirubicin (about 19%), epirubicinol and other metabolites. Over the same period, only 9 to 12% of the dose is excreted in the urine, also as unchanged drug and metabolites. At 72 hours, figures are about 43% in bile and about 16% in urine.

Indications

Epirubicin has produced significant therapeutic responses in a number of neoplastic diseases, among which:

- carcinoma of the breast
- carcinoma of the ovary
- small cell lung cancer
- non-small cell lung cancer
- carcinoma of the stomach
- transitional cell bladder cancer
- soft-tissue and bone sarcomas
- non-Hodgkin's lymphoma and Hodgkin's disease
- hormone-refractory prostatic carcinoma
- Epirubicin has also shown antitumour activity in the following tumours:
 - carcinoma of the oesophagus
 - primary hepatocellular carcinoma
 - pancreatic carcinoma
 - carcinoma of the head and neck
 - acute leukaemias and multiple myeloma

Dosage and Administration

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 fully trained with this technique.

Intravenous 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 (e.g. given as a single agent or in combination with other cytotoxic drugs) and according to the therapeutic indication (e.g. in the treatment of lung cancer epirubicin is also used at doses higher than conventional).

Conventional dose

When epirubicin is used as a single agent, the recommended dose per cycle in adults is 60-90 mg/m^2 of body surface area. The total dose per cycle may be given in one instance 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 to four 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): 120 mg/m^2 day 1, every three weeks.

Non-small cell lung cancer (squamous large cell and adeno-carcinoma, previously untreated): 135 mg/m^2 day 1 or 45 mg/m^2 days 1, 2, 3 every three weeks.

Breast cancer: Doses up to 135 mg/m^2 as single agent and 120 mg/m^2 in combination, every 3-4 weeks proved to be effective and well tolerated in the treatment of breast cancer. In the adjuvant treatment of early breast cancer patients with positive lymph nodes, doses ranging from 100 mg/m^2 to 120 mg/m^2 every 3-4 weeks are recommended.

Low doses (60-75 mg/m^2 , or 105-120 mg/m^2 for *high dose* schedules) or a longer interval between cycles are recommended for heavily pretreated patients, or in the presence of neoplastic bone marrow infiltration (see also Warnings and Precautions). If epirubicin is used in combination with other cytotoxic drugs with potentially overlapping toxicities, the recommended dose per cycle might need to be reduced accordingly.

Renal Dysfunction: While no specific dose recommendation can be made based on the limited available data in patients with renal impairment, lower starting doses should be considered in

patients with severe renal impairment (serum creatinine >5 mg/dL).

Hepatic Dysfunction: Since the major route of elimination of epirubicin is the hepatobiliary system, the dosage must be reduced in patients with impaired liver function in order to avoid an increase of overall toxicity. Dose reductions are recommended in patients with the following serum chemistry values:

- Bilirubin 1.2 to 3 mg/dL or AST 2 to 4 times upper limit of normal:
½ of recommended starting dose.
- Bilirubin > 3 mg/dL or AST > 4 times upper limit of normal:
¼ of recommended starting dose.

Intravesical Administration

For the treatment of papillary transitional cell carcinoma of the bladder, a therapy of 8 weekly instillations of 50 mg (in 25-50 mL of saline solution) is recommended. In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg is advised. For carcinoma-in-situ, depending on the individual tolerability of the patient, the dose may be increased up to 80 mg. For prophylaxis of recurrences after transurethral resection of superficial tumours, 4 weekly administrations of 50 mg followed by 11 monthly instillations at the same dosage are recommended.

Incompatibilities

EPICCORD should not be mixed with other drugs. Contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug. EPICCORD should not be mixed with heparin due to chemical incompatibility which may lead to precipitation.

Instructions for Use/Handling

EPICCORD is a ready to use solution. Storage of the ready-to-use solution for injection at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after two to a maximum of four hours equilibration at room temperature (15° – 25°C).

Intravenous administration: EPICCORD is not active when given orally and should not be injected intramuscularly or intrathecally. Intravenous administration of EPICCORD should be performed with caution. It is recommended to give the drug via the tubing of a freely-running intravenous infusion (0.9% sodium chloride or 5% dextrose solution). To minimise the risk of thrombosis or perivenous extravasation, the usual infusion times range between 3 and 20 minutes depending upon the dosage and volume of infusion solution. Extravasation of EPICCORD from the vein during injection may give rise to severe tissue lesions, even 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 (see Warnings and Precautions). Venous sclerosis may result from injection into small vessels or repeated injections into the same

vein.

The drug should be used within 24 hours of first penetration of the rubber stopper.

Discard any unused solution.

Intravesical administration: EPICCORD should be instilled using a catheter and be retained intravesically for 1 hour. During instillation the patient should be rotated to ensure that the vesical mucosa of the pelvis receives the most extensive contact with solution. To avoid undue dilution with the urine, the patient should be instructed not to drink any fluid in the twelve hours prior to instillation. The patient should be instructed to void at the end of this time. Intravesical administration is not suitable for the treatment of invasive tumours which have penetrated the bladder wall.

Protective measures: The following protective recommendations are given due to the toxic nature of this substance.

- Personnel should be trained in good technique and handling;
- Pregnant staff should be excluded from working with this drug;
- Personnel handling EPICCORD should wear protective clothing: goggles, gowns and disposable gloves and masks;
- All items used for, administration or cleaning, including gloves, should be placed in high-risk, waste-disposal bags for high temperature incineration.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water.
- All cleaning materials should be disposed of as indicated previously.
- In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush.
- In case of contact with the eye(s), hold back the eyelid of the affected eye(s) and flush with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

Contraindications

Hypersensitivity to epirubicin or any other component of the product, other anthracyclines or anthracenediones.

Intravenous (IV) use:

Situations in which patients should not be treated with intravenous epirubicin are:

- persisting myelosuppression or severe stomatitis from previous cytotoxic treatments;
- presence of generalised infections;
- marked liver function impairment;

- current or previous history of severe arrhythmias and myocardial insufficiency; previous myocardial infarction;
- previous treatments with anthracyclines up to their maximum cumulative doses;
- Pregnancy and lactation (see also Warnings and Precautions, Pregnancy and Lactation).

Intravesical use:

Contraindications for intravesical use are:

- invasive tumours that have penetrated the bladder wall;
- urinary infections;
- inflammation of the bladder;
- catheterisation problems;
- haematuria

Warnings and Precautions

General: Epirubicin should be administered only under the supervision of qualified physicians experienced in cytotoxic therapy.

Patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia, and generalised infections) of prior cytotoxic treatment before beginning treatment with epirubicin.

While treatment with high doses of epirubicin (≥ 90 mg/m² every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/m² every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucositis may be increased. Treatment with high doses of epirubicin does require special attention for possible clinical complications due to profound myelosuppression.

Cardiac Function - Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (acute) or late (delayed) events.

Early (Acute) Events. Early cardiotoxicity of epirubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia, and 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 a consideration for the discontinuation of epirubicin treatment.

Late (Delayed) Events. Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin or within 2 to 3 months after treatment termination, but later events several months to years after completion of treatment have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Life-

threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin in excess of 900 mg/m²; this cumulative dose should only be exceeded with extreme caution.

Cardiac function should be assessed before patients undergo treatment with epirubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of epirubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m² epirubicin should be exceeded only with extreme caution.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/ pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of other drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab). Anthracyclines including epirubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines 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. The half-life of trastuzumab is approximately 28.5 days and may persist in the circulation for up to 24 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 24 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with epirubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.

It is probable that the toxicity of epirubicin and other anthracyclines or anthracenediones is additive.

Haematologic Toxicity - As with other cytotoxic agents, epirubicin may produce myelosuppression. Haematologic profiles should be assessed before and during each cycle of therapy with epirubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopenia and neutropenia are generally more severe with high-dose schedules, reaching the nadir in most cases between days 10 and 14 after drug administration;

this is usually transient with the WBC/neutrophil counts returning to normal values in most cases by day 21. Thrombocytopenia and anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia, or death.

Secondary Leukaemia - Secondary leukaemia, with or without a preleukaemic phase, has been reported in patients treated with anthracyclines, including epirubicin. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukaemias can have a 1- to 3-year latency period.

Carcinogenesis, Mutagenesis & Impairment of Fertility (see Pregnancy and Lactation) - Epirubicin, like other anthracyclines and cytotoxic drugs, has been found to be carcinogenic in rats. Epirubicin was genotoxic in most of the *in vitro* or *in vivo* tests performed, toxic to the reproductive organs, and embryotoxic in rats. No malformations were seen in either rats and rabbits, however, epirubicin, like other anthracyclines and cytotoxic drugs, must be considered potentially teratogenic.

Epirubicin is mutagenic, clastogenic, and carcinogenic in animals and could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should use effective contraceptive methods. Epirubicin may cause amenorrhoea or premature menopause in premenopausal women.

Gastrointestinal - Epirubicin is emetogenic. Mucositis/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Liver Function - The major route of elimination of epirubicin is the hepatobiliary system. Serum total bilirubin, AST levels should be evaluated before and during treatment with epirubicin. Patients with elevated bilirubin or AST may experience slower clearance of drug with an increase in overall toxicity. Lower doses are recommended in these patients (see Dosage and Administration). Patients with severe hepatic impairment should not receive epirubicin (see Contraindications).

Renal Function - Serum creatinine should be assessed before and during therapy. Dosage adjustment is necessary in patients with serum creatinine > 5 mg/dL (see Dosage and Administration).

Effects at Site of Injection - Phlebosclerosis may result from injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimise the risk of phlebitis/thrombophlebitis at the injection site (see Dosage and Administration, Instruction for Use/Handling).

Extravasation - Extravasation of epirubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of epirubicin, the drug infusion should

be immediately terminated.

Other - As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal) have been coincidentally reported with the use of epirubicin.

Tumour-Lysis Syndrome - Epirubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism which accompanies the rapid drug-induced lysis of neoplastic cells (tumour-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimise potential complications of tumour-lysis syndrome.

Immunosuppressant Effects/Increased Susceptibility to Infections - Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including epirubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving epirubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Epirubicin may impart a red colour to the urine for one-two days after administration. Patients have to be advised that such an event should not be cause for alarm.

Pregnancy and Lactation (see Carcinogenesis, Mutagenesis & Impairment of Fertility)

There is no conclusive information as to whether epirubicin may adversely affect human fertility, or cause teratogenesis. Experimental data in animals, however, suggest that epirubicin may cause fetal harm when administered to a pregnant woman. There are no studies in pregnant women. EPICCORD should not be administered to patients who are pregnant and women of child-bearing potential who have to undergo epirubicin therapy should be apprised of the potential hazard to the fetus and should be advised to avoid becoming pregnant during treatment.

It is not known 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, women treated with EPICCORD should not breastfeed.

Additional Warnings and Precautions for Other Routes of Administration

Intravesical route - Administration of epirubicin may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, haematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterisation problems (e.g., urethral obstruction due to massive intravesical tumours) [see Contraindications].

Intra-arterial route - Intra-arterial administration of epirubicin (transcatheter arterial embolisation for the localised or regional therapies of primary hepatocellular carcinoma or liver metastases) may produce (in addition to systemic toxicity qualitatively similar to that observed

following intravenous administration of epirubicin) localised or regional events which include gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to drug-induced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue.

Adverse Effects

Clinical Trials:

A large number of clinical trials with epirubicin, administered at both conventional and high doses in different indications, have been conducted. Serious drug-related adverse events that occurred during clinical trials are listed below.

Haematologic: leukopenia, neutropenia, anaemia, thrombocytopenia

Endocrine: amenorrhoea, hot flushes

Body as a Whole: malaise/asthenia, fever

Gastrointestinal: nausea/vomiting, mucositis/stomatitis, diarrhoea, anorexia

Cardiovascular: asymptomatic drops in left ventricular ejection fraction, congestive heart failure

Ocular: conjunctivitis/keratitis

Skin: alopecia, local toxicity, rash/itch, skin changes

Liver: changes in transaminase levels

Other: infection, acute lymphocytic leukaemia, acute myelogenous leukaemia, azoospermia

Postmarketing Surveillance:

Gastrointestinal: pain or burning sensation, erythema, erosions, ulcerations, bleeding, dehydration, hyperpigmentation of the oral mucosa

Cutaneous: flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction)

Hypersensitivity Reactions: urticaria, anaphylaxis, fever, chills, shock

Vascular: phlebitis, thrombophlebitis

Urological: red colouration of urine for 1 to 2 days after administration. Chemical cystitis, sometimes haemorrhagic, and bladder constriction have been observed following intravesical use

Interactions

Epirubicin can be used in combination with other cytotoxic drugs. When using epirubicin as a part of chemotherapy regimens which combine drugs with similar pharmacologic effects (i.e. cytotoxicity), additive toxicity is likely to occur. Such additive toxicity has to be taken into consideration especially with regard to the bone marrow/haematologic and gastrointestinal effects (see Warnings and Precautions). The concomitant use of epirubicin and other drugs which have been reported as cardiotoxic (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes, trastuzumab), as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blocker drugs) requires monitoring of cardiac function throughout therapy.

Epirubicin is extensively metabolised by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicin metabolism or pharmacokinetics and, as a result, efficacy and/or toxicity.

Cimetidine increased the AUC of epirubicin by 50% and should be stopped during treatment with epirubicin.

When given prior to epirubicin, paclitaxel can cause increased plasma concentrations of unchanged epirubicin. Coadministration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when epirubicin was administered prior to the taxane.

Overdosage

A 36-year-old man with non-Hodgkin's lymphoma received a daily 95 mg/m² dose of epirubicin injection for 5 consecutive days. Five days later, he developed bone marrow aplasia, grade 4 mucositis and gastrointestinal bleeding. No signs of acute cardiac toxicity were observed. He was treated with antibiotics, colony-stimulating factors and antifungal agents and recovered completely. A 63-year-old woman with breast cancer and liver metastasis received a single 320 mg/m² dose of epirubicin, which resulted in hyperthermia, multiple organ failure (respiratory and renal), lactic acidosis, increased lactate dehydrogenase and anuria, and death within 24 hours of administration.

Additional instances of administration of doses higher than recommended have been reported at doses ranging from 150 to 250 mg/m². The observed adverse events in these patients were qualitatively similar to known toxicities of epirubicin. Most of the patients recovered with appropriate supportive care.

Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression (mainly leukopenia and thrombocytopenia) within 10-14 days and also gastrointestinal toxic effects (mainly mucositis).

If an overdose occurs, supportive treatment (including antibiotic therapy, blood and platelet transfusions, colony-stimulating factors and intensive care as needed) should be provided until

the recovery of toxicities. Delayed cardiac failure may occur 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.

Contact the Poisons Information Centre for advice on the management of overdose.

Pharmaceutical Precautions

EPICCORD solution should be kept refrigerated at 2°-8°C until ready to use. The solution is stable for 24 hours at room temperature; discard unused portion.

EPICCORD solution should not be used after 24 hours following the removal from the refrigerator.

Shelf life of the product as package for sale:

2 years

Shelf life after first opening the container:

The vials are for single use only and any unused portion must be discarded after use. From a microbiological point of view, the product should be used immediately after the first penetration of the rubber stopper. If not used immediately, in use storage times and conditions are the responsibility of the user.

Shelf life after dilution of the solution for injection:

Epirubicin Hydrochloride 2 mg/ml Injection may be further diluted, under aseptic conditions, in Glucose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

All material used for preparation, administration or otherwise coming into contact with Epirubicin should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

Medicine Classification

Prescription Medicine.

Package Quantities

EPICCORD Solution: Vials, 10 mg/5 mL, packs of 1
20 mg/10 mL, packs of 1
50 mg/25 mL, packs of 1
200 mg/100 mL, packs of 1

Further Information

Preclinical Safety Data

The LD₅₀ of epirubicin was 29.3 and 14.2 mg/kg for mice and rats, respectively, and about 2.0 mg/kg for dogs. The main target organs after a single dose were the haemolymphopoietic system and, especially in dogs, the G.I. tract. The toxic effects after repeated administrations of epirubicin were investigated in rats, rabbits and dogs. The main target organs of epirubicin in these animal species were the haemolymphopoietic system, G.I. tract, kidney, liver and male and female reproductive organs. Concerning the heart, subacute and cardiotoxicity studies indicated that epirubicin was cardiotoxic in all the laboratory species tested. No noteworthy effects were seen in rats given epirubicin during the peri - and post-natal periods up to the dose of 0.15 mg/kg/day for the mothers and 0.50 mg/kg/day for the offspring. A local safety study in mice and rats showed that extravasation of the drug causes tissue necrosis.

The specificity of epirubicin toxicity appears to be related primarily to proliferative activity of normal tissue. Thus, bone marrow, gastrointestinal tract, lymphoid organs and the gonads are the main normal tissues damaged. Degenerative or functional alterations in liver and kidneys were also seen in animals dosed with epirubicin.

Like most other antitumour and immunosuppressant agents, epirubicin, under experimental conditions, has mutagenic properties and is carcinogenic in laboratory animals (see Warnings and Precautions, Carcinogenesis, Mutagenesis & Impairment of Fertility, Pregnancy and Lactation).

Toxicity studies in animals have indicated that on a weight (mg per mg) basis epirubicin has a better therapeutic index and less systemic and cardiac toxicity than doxorubicin.

Name and Address

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Date of Preparation

October 20, 2010