

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin Hydrochloride 2 mg/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2 mg Epirubicin hydrochloride.

Each 5/10/25/50/100 ml vial contains 10/20/50/100/200 mg Epirubicin hydrochloride.

Excipient: Contains sodium 3.54 mg/ml (0.154 mmol).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion

A clear red solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epirubicin is used in the treatment of a range of neoplastic conditions including;

- Carcinoma of the breast
- Gastric cancer
- Ovarian cancer
- Lung cancer in non-pretreated patients [Small cell lung cancer (SCLC)]

When administered intravesically, epirubicin has been shown to be beneficial in the treatment of

- Papillary transitional cell carcinoma of the bladder
- Carcinoma-in-situ of the bladder.
- Prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection

4.2 Posology and method of administration

Epirubicin is for intravenous or intravesical use only.

The safety and efficacy of epirubicin in children has not been established

Intravenous administration

It is advisable to administer epirubicin via the tubing of a free-running intravenous saline infusion after checking that the needle is properly placed in the vein. Care should be taken to avoid extravasation (see section 4.4). In case of extravasation, administration should be stopped immediately.

Conventional dose

Dosage regimen for conventional doses

When epirubicin is used as a single antineoplastic agent, the recommended dose for adults is 60-90 mg/m² of body surface area to be administered via intravenous injection over 5 to 10 minutes at 21-day intervals, depending on the blood and bone marrow conditions.

If signs of toxicity, including severe neutropenia/neutropenic fever and thrombocytopenia occur (which could persist at day 21), dose modification or postponement of the subsequent dose may be required.

High dose

Dosage regimen for high doses

Lung cancer

Epirubicin as a single agent in the treatment of lung cancer with high doses must be used according to the following schemes:

- Small cell lung cancer (SCLC) in non-pretreated patients: 120 mg/m² on day 1, every three weeks.

The drug must be administered as an intravenous bolus over 5-10 minutes or as an intravenous infusion over a maximum of 30 minutes.

Breast Cancer

In the adjuvant treatment of initial breast cancer with positive lymph nodes, the recommended doses vary from 100 mg/m² to 120 mg/m² administered every 3-4 weeks.

Lower doses (60-75 mg/m² or 105-120 mg/m² in high dosage regimens) are recommended for patients with reduced bone marrow reserves due to previous chemo-and/or radiotherapy treatments, elderly age, or with bone marrow neoplastic. The total dose per cycle can be divided over 2-3 consecutive days.

The following doses of epirubicin are commonly used in monotherapy and combination chemotherapy for various tumours, as shown:

	Epirubicin Dose (mg/m ²) ^a	
Cancer Indication	Monotherapy	Combination Therapy
Ovarian cancer	60–90	50–100 ^b
Gastric cancer	60–90	50
Small cell lung cancer (SCLC)	120	120 ^b
Bladder cancer	50 mg/50 ml or 80 mg/50 ml (carcinoma in situ) Prophylaxis: 50 mg/50 ml weekly for 4 weeks then monthly for 11 months	
Breast cancer		100-120 ^c

a Doses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals.

b If used in combination with other anticancer drugs, the doses should be appropriately reduced.

c Lower doses (60-75 mg/m² or 105-120 mg/m² in high dosage regimens) are recommended for patients with reduced bone marrow function.

Impaired liver function

Most important elimination pathway of the drug is the hepatobiliary system, a dose reduction of Epirubicin is suggested for patients who have impaired liver function, in order to avoid global toxicity.:

Generally speaking, when blood bilirubin levels are between 1.4-3 mg/100 ml and bromosulfophthalein (BSF) retention is 9-15%, half the normal drug dose is recommended.

Serum Bilirubin	AST*	Dose Reduction
1.4 – 3 mg/100 ml		50%
> 3 mg/100 ml	> 4 times upper normal limit	75%

*AST – aspartate aminotransferase

If bilirubin levels and BSF retention are higher still, a quarter of the normal dose is recommended.

Impaired renal function

Moderate impairment of renal function does not seem to require a dose reduction in view of the limited amount of epirubicin excreted by this route. Lower starting doses should be considered in patients with severe renal impairment (serum creatinine > 450µmol/l).

Intravesical administration

In the treatment of transitional cell papillary carcinoma. Weekly instillations of 50 mg (in 25-50 mL saline solution or distilled sterile water) are recommended, to be repeated every eight weeks; in case of local toxicity (chemical cystitis), the unit dose must be reduced to 30 mg.

In the treatment of in-situ carcinoma, the dose may be increased to 80 mg depending on individual tolerability.

In the prophylaxis of relapses after transurethral resection of superficial tumors, weekly instillations of 50 mg are recommended, to be repeated every four weeks, followed by monthly instillations at the same dose for up to one year.

Method of administration

Epirubicin is not active via the oral route and must not be administered intramuscularly or intrathecally.

DILUTION TABLE FOR BLADDER INSTILLATION SOLUTIONS

Dose Epirubicin required	Volume of 2 mg/ml epirubicin hydrochloride injection	Volume of diluent sterile water for injection or 0.9% sterile saline	Total volume for bladder installation
30 mg	15 ml	35 ml	50 ml
50 mg	25 ml	25 ml	50 ml
80 mg	40 ml	10 ml	50 ml

Intravenous administration

It is advisable to perform intravenous administration over 5-10 minutes through the infusion tube of a free-running saline solution infusion, after having ensured that the needle is perfectly positioned in the vein. This technique reduces the risk of extravasation of the drug and ensures flushing of the vein at the end of administration.

In case of extravasation of Epirubicin during administration, there is a risk of tissue lesions, including necrosis.

Venous sclerosis may occur when the injection is administered into small vessels or is repeated in the same vein.

Intravesical administration

Epirubicin for instillation via a catheter must be kept in situ for an hour. The patient should be instructed not to drink any fluid in the 12 hours prior instillation. During instillation, it may be advisable to rotate the patient's pelvis to ensure broader contact of the solution with the bladder mucosa.

4.3 Contraindications

Epirubicin is contraindicated in:

- Patients who have demonstrated hypersensitivity to the active substance or to any of the excipients listed in section 6.1, other anthracyclines or anthracenediones.
- Breast-feeding

Intravenous use:

- Patients with persistent myelosuppression
- severe hepatic impairment
- severe myocardial insufficiency
- recent myocardial infarction
- severe arrhythmias
- previous treatments with maximum cumulative doses of epirubicin and/or other anthracyclines and anthracenediones (see section 4.4)
- patients with acute systemic infections
- unstable angina pectoris
- cardiomyopathy

Intravesical use:

- Urinary tract infections.
- Invasive bladder tumours.
- Catheterisation problems.
- Inflammation of the bladder.
- Hematuria

4.4 Special warnings and precautions for use

General

Epirubicin hydrochloride must be administered under the supervision of doctors who are experts in the use of cytotoxic therapies.

Before starting treatment with epirubicin hydrochloride, patients must recover from the acute toxicity of the previous cytotoxic therapy (such as stomatitis, neutropenia, thrombocytopenia, and generalised infections).

While treatment with high doses of epirubicin hydrochloride (e.g., ≥ 90 mg/m² every 3 or 4 weeks) causes undesirable effects that are generally similar to those observed with standard doses (< 90 mg/m² every 3 or 4 weeks), neutropenia and stomatitis mucositis may be more severe. Treatment with high doses of epirubicin hydrochloride requires particular care because of the possible complications due to severe myelosuppression.

Cardiac Function - Cardiotoxicity is a risk of treatment with anthracyclines, which can manifest with acute delayed events.

Acute toxicity. The immediate cardiotoxicity of epirubicin hydrochloride manifests principally as sinus tachycardia and/or ECG tracing abnormalities such as non-specific ST-T changes. There have also been reports of manifestations principally as tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia, and bradycardia, as well as bundle branch block and atrioventricular block. These effects do not usually anticipate the subsequent manifestation of delayed cardiotoxicity, rarely have clinical significance, and do not generally require interruption of treatment with epirubicin hydrochloride.

Delayed toxicity. Delayed cardiotoxicity usually manifests in the advanced phases of treatment or between the second and third months following conclusion of treatment, but there have also been reports of later manifestation (several months or years after end of therapy). Delayed cardiomyopathy is manifest via a reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Potentially fatal heart failure is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of medicinal product.

The risk of developing congestive heart failure increases rapidly with the increase of total cumulative doses of over 900 mg/m² of epirubicin hydrochloride; this cumulative dose must be exceeded only with extreme caution (see section 5.1).

Cardiac function must be evaluated prior to starting treatment with epirubicin hydrochloride and must be monitored during therapy to minimise the risk of serious cardiac damage. This risk can be reduced by regularly monitoring LVEF during treatment the first sign of impairment of cardiac function appears. The quantitative methods indicated regularly monitoring cardiac function (LVEF evaluation) are MUGA (multi-gated radionuclide angiography) scans or echocardiography. Baseline evaluation of cardiac function with an ECG or MUGA scan or echocardiography is recommended, particularly in patients with risk factors due to increased cardiotoxicity. A second evaluation of LVEF using MUGA or echocardiography must be performed, especially with high cumulative anthracycline doses. The monitoring technique used for evaluation must be constant during the follow-up period.

In view of the risk of cardiomyopathy, a cumulative dose of 900 mg/m² of epirubicin hydrochloride must only be exceeded with extreme caution.

The risk factors for cardiac toxicity include active or silent cardiovascular disease, previous radiation therapy or concomitant radiation therapy on the pericardial mediastinal area, previous treatment with other anthracyclines or anthracenediones, concomitant use of medicinal products that suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab) (see section 4.5) with an increased risk in the elderly.

Cardiac failure (New York Heart Association -NYHA class II-IV) was observed in patients receiving therapy trastuzumab alone or in combination with anthracyclines such as epirubicin. This can be moderate or severe and has been associated with death.

Trastuzumab and anthracyclines like epirubicin must not usually be used in combination, except in well-controlled clinical studies with cardiac monitoring. Even patients who have been previously treated with anthracyclines are at risk of cardiotoxicity when treated with trastuzumab, although the risk is lower than that observed with the concomitant use of trastuzumab and anthracyclines.

It has been reported that trastuzumab has a variable half-life. Trastuzumab can remain in the circulation for up to seven months after interruption of treatment. Patients who receive anthracyclines, such as epirubicin, can be at increased risk of cardiotoxicity after interruption of treatment with trastuzumab. Whenever possible, the doctor must avoid anthracycline-based therapies for up to seven months after interruption of trastuzumab. If anthracyclines like with epirubicin are used, the patient's cardiac function must be carefully monitored.

If symptomatic cardiac failure develops during treatment with trastuzumab, after treatment with epirubicin hydrochloride, these must be treated with standard medical therapy.

Cardiac function must be carefully monitored in patients who take high cumulative doses and in those with risk factors. However, cardiotoxicity with epirubicin hydrochloride can occur with lower cumulative doses in the presence or absence of risk factors for cardiac toxicity.

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

Blood Toxicity Like with other cytotoxic agents, epirubicin can cause myelosuppression. The blood profile, including a differential WBC count, must be evaluated before and during each treatment cycle with epirubicin. Blood toxicity manifests mainly as reversible and dose-dependent leukopenia and/or granulocytopenia (neutropenia), which represent the most common manifestations of the acute dose-limiting toxicities of this medicinal products. Leucopenia and neutropenia are usually more severe with high treatment doses, with the nadir occurring in most cases between the 10th and 14th day following administration of the drug; this is generally transient and the WBC/neutrophil counts return to normal within 21 days. Thrombocytopenia and anaemia may also occur. The clinical consequence of severe myelosuppression are: fever, infections, sepsis/septicaemia, septic shock, bleeding, tissue hypoxia, or death.

Secondary Leukaemia – There have been reports of secondary leukaemia, with or without a preleukaemic phase, in patients treated with anthracyclines, (including epirubicin). Secondary leukaemia is more common when these medicinal products are administered in combination with antineoplastic agents that damage DNA, in combination with radiotherapy, when patients have been heavily pre-treated with cytotoxic agents, or when doses of the anthracyclines have been increased. These leukaemia's can have a latency period that varies between one and three years. (See section 5.1).

Gastrointestinal tract - Epirubicin hydrochloride induces vomiting. Mucositis/stomatitis usually occur immediately after drug administration and, if severe, can progress in a few days to ulceration of the mucous membranes. In the majority of patients, recovery from these adverse events occurs within the third week of therapy.

Liver Function - The main route of elimination for epirubicin hydrochloride is the hepatobiliary system. Total serum bilirubin levels and AST must be measured before and during treatment with epirubicin hydrochloride. Patients with high bilirubin or AST may show lower clearance of the drug with increased global toxicity. Lower doses are recommended for these patients (see sections 4.2 and 5.2). Patients with severe hepatic damage must not take epirubicin hydrochloride (see section 4.3).

Renal Function - Serum creatinine must be measured before and during therapy. A dose adjustment is necessary in patients with serum creatinine level > 5 mg/dL (see section 4.2).

Effects at Site of Injection - Injection into a small vessel or repeat injections in the same vein can cause phlebosclerosis. The risk of phlebitis/thrombophlebitis at the site of injection can be minimised by following the recommended administration procedures (see section 4.2).

Extravasation - Extravasation of epirubicin hydrochloride during intravenous injection can cause local pain, serious tissue injuries (onset of vesicles, severe cellulitis) and necrosis. If signs or symptoms of extravasation appear during an intravenous administration of epirubicin hydrochloride, the infusion of the medicinal product must be interrupted immediately. The undesirable effects resulting from extravasation of anthracyclines can be prevented or reduced by immediately using a specific treatment e.g. dexrazoxane (refer to the information for use of the product). The patient's pain can be alleviated by cooling the area and keeping it cold using hyaluronic acid and DMSO. The patient must be monitored carefully during the subsequent period cause necrosis may occur several weeks after extravasation. Consult a plastic surgeon about the possibility of removal.

Other - Like with other cytotoxic agents, there have been reports of thrombophlebitis and thromboembolic events, including pulmonary embolism in some cases fatal with the use of epirubicin hydrochloride.

Tumour-Lysis Syndrome - Epirubicin hydrochloride can cause hyperuricemia as a consequence of the extensive catabolism of purines associated with the rapid tumour cell lysis induced by the medicinal product (tumour-lysis syndrome). Blood levels of uric acid, potassium, calcium phosphate, and creatinine must be measured after start of treatment. Hydration, alkalinisation of urine, and prophylaxis with allopurinol for preventing uric acid in blood can minimise the potential complications of tumour-lysis syndrome.

Immunosuppressant Effects/Increased Susceptibility to Infections- The administration of live vaccines or live-attenuated vaccines to patients immunosuppressed by chemotherapy agents, including epirubicin hydrochloride, can cause serious or fatal infections (see section 4.5).

Vaccination with live vaccines must be avoided in patients receiving epirubicin hydrochloride. Killed or inactivated vaccines can be administered; however, the response to these vaccines may be reduced.

Reproductive system: Epirubicin hydrochloride can cause genotoxicity. Men and women treated with epirubicin hydrochloride must use appropriate methods of contraception. If appropriate and possible, patients who wish to have children after completion of therapy must request a genetic consultation.

Intravesical use - Administration of epirubicin hydrochloride can cause chemical cystitis symptoms (such as dysuria, polyuria, nocturia, strangury, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Particular care must be paid to catheterisation problems (such as urethral obstruction caused by large intravesical tumours).

Intra-arterial route - Intra-arterial administration of epirubicin hydrochloride (transcatheter arterial embolisation for the localized 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 hydrochloride) localized 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.

Excipient warning

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin hydrochloride can also be used in combination with other anticancer chemotherapy agents. Cumulative toxicity may manifest with effects on the bone marrow/blood and gastro-intestinal system (see section 4.4). The use of epirubicin hydrochloride in chemotherapy combined with other potentially cardiotoxic agents, as well as the concomitant use with cardioactive compounds (e.g., calcium channel blockers), requires cardiac function monitoring for the entire duration of treatment.

Epirubicin hydrochloride is extensively metabolised in the liver. Changes in the hepatic metabolism induced by concomitant therapies can affect the metabolism of epirubicin hydrochloride, its pharmacokinetics, therapeutic efficacy and/or toxicity (see section 4.4).

Anthracyclines including epirubicin, must not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is carefully monitored. Patients taking anthracyclines after the interruption of treatment with other cardiotoxic agents, particularly those with a long half-life such as trastuzumab, can also be exposed to an increased risk of onset of cardiotoxicity. Trastuzumab has a variable half-life and can remain in the circulatory system for up to seven months. Therefore, if possible, doctor must avoid an anthracycline-based therapy for up to seven months after the end of treatment with trastuzumab. If anthracyclines are used before this period, cardiac function must be monitored carefully.

Vaccination with live vaccines must be avoided in patients taking epirubicin hydrochloride. Killed or inactivated vaccines can be administered; however, the response to these vaccines may be reduced.

Cimetidine increases the AUC of epirubicin hydrochloride by 50% and the use of this medicinal product must be interrupted during treatment with epirubicin hydrochloride

When given prior to epirubicin hydrochloride, paclitaxel can cause increased plasma concentrations of unchanged epirubicin hydrochloride and its metabolites, the latter being, however, neither toxic nor active. Coadministration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin hydrochloride when epirubicin hydrochloride was administered prior to the taxane.

This combination may be used if using staggered administration between the two agents. Infusion of epirubicin hydrochloride and paclitaxel should be performed with at least a 24 hour interval between the 2 agents.

Dexverapamil may alter the pharmacokinetics of epirubicin hydrochloride and possibly increase its bone marrow depressant effects.

One study found that docetaxel may increase the plasma concentrations of epirubicin hydrochloride metabolites, when administered immediately after epirubicin hydrochloride .

Quinine can accelerate the initial distribution of epirubicin hydrochloride from blood in to the tissues and may influence the partitioning of red blood cells by epirubicin hydrochloride .

The co-administration of interferon α 2b can cause a reduction in the terminal elimination half-life of both total and partial clearance of epirubicin hydrochloride.

The possibility of a marked disturbance of haematopoiesis needs to be kept in mind with a (pre-) treatment with medications which influence the bone marrow (i.e. cytostatic agents, sulphonamide, chloramphenicol, diphenylhydantoin, amidopyrine-derivate, antiretroviral agents).

Patients who receive therapy in combination with anthracyclines and dexrazoxane may suffer an increase in myelosuppression.

4.6 Fertility, pregnancy and lactation

(See section 5.3)

Fertility

Epirubicin hydrochloride could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin hydrochloride must use effective contraceptive methods during treatment and for at least 4 months after last dose. If appropriate and possible, should request a consultation on the possibility of preserving sperm as the therapy could cause irreversible infertility.

Epirubicin hydrochloride may cause amenorrhea or early menopause in premenopausal women.

Pregnancy

Women of childbearing potential must be advised to avoid becoming pregnant during treatment and must use effective methods of contraception during treatment and for at least 7 months after last dose.

Experimental animal data suggest that epirubicin hydrochloride can cause foetal damage when administered to pregnant women. If epirubicin hydrochloride is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus.

There are no studies on pregnant women. Epirubicin hydrochloride must only be used during pregnancy if the potential benefit justifies the potential risk for the foetus.

Breast-feeding

It is not known whether epirubicin hydrochloride is excreted in human breast 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 hydrochloride, mothers should discontinue nursing prior to taking this drug.

4.7 Effects on ability to drive and use machines

There have been no reports of particular adverse events relating to effects on ability to drive and to use machines.

4.8 Undesirable effects

The following adverse effects have been observed and reported during treatment with epirubicin with the following frequencies:

very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

Over 10% of patients treated can develop undesirable effects. The most common undesirable effects are myelosuppression, gastrointestinal disorders, anorexia, alopecia and infections

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	Infection, Conjunctivitis		Sepsis,* pneumonitis*			Septic shock cellulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Acute myeloid leukaemia, Acute lymphocytic leukaemia			
Blood and lymphatic system disorders	Myelosuppression (Anaemia, Leukopenia, Neutropenia, granulocytopenia, Thrombocytopenia, Febrileneutropenia)					
Immune system disorders				Hypersensitivity [§] Anaphylacticreaction*		
Metabolism and nutrition disorders		Decreased appetite Dehydration*		Hyperuricaemia*		
Nervous system disorders	Burning sensation [§]			Dizziness		
Eye disorder	Keratitis					

ders						
Cardiac disorders		Ventricular tachycardia, Atrioventricular block, Bundlebranch block, Bradycardia, congestive heart failure		Cardiotoxicity		
Vascular disorders	Hot flushes, Phlebitis*	Bleeding*, Flushing*	Embolism, Embolism arterial,* Thrombophlebitis*			Shock*
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism*			
Gastrointestinal disorders	Nausea, Vomiting, Stomatitis, Mucosal inflammation, Diarrhoea	Gastrointestinal pain,* Gastrointestinal erosion,* Oesophagitis Gastrointestinal ulcer*	Gastrointestinal haemorrhage*			Abdominal discomfort, Oral mucosa erosion, Mouth ulceration, oral pain, Burning sensation of the mucous membranes, Mouth haemorrhage, Pigmentation buccal*
Skin and subcutaneous tissue disorders	Alopecia, Skin toxicity	Rash/Pruritus, Nail pigmentation,* Skin disorder, Skin hyperpigmentation*	Urticaria* Erythema*			Photosensitivity reaction*
Renal and urinary disorders	Chromaturia**	Pollakiuria§				
Reproductive system and breast disorder	Amenorrhoea			Azoospermia		

ders						
General disorders and administration site conditions	Malaise, Pyrexia*	Administration site erythema, Chills*	Asthenia			Phlebosclerosis, Pain, Soft tissue necrosisε
Investigations	Transaminases abnormal	Ejection fraction decreased				
Injury, poisoning and procedural complications	Chemical cystitis*§					Recall phenomenon*Δ
* ADR identified post-marketing. † Red coloration of urine for 1 to 2 days after administration. § Following intravesical administration. Δ Hypersensitivity to irradiated						

skin (radiation-recall reaction).						
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Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRC Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

An acute overdose with epirubicin hydrochloride can cause severe myelosuppression (mainly leucopenia and thrombocytopenia), toxic gastrointestinal effects (mainly mucositis) and acute cardiac complications. Delayed cardiac failure has been observed with anthracyclines, which manifested from several months to years after completion of treatment (see section 4.4). Patients must be carefully monitored. If there are signs of cardiac failure, patients must be treated according to conventional guidelines.

Treatment:

Symptomatic. Epirubicin cannot be removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic antibiotics – anthracyclines.

ATC code: L01D B03.

The mechanism of action of epirubicin hydrochloride 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 hydrochloride has proved to be active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcomas SA180 (solid and ascitic forms), B16 melanoma, breast cancer, Lewis lung carcinoma colon cancer (38) and also human tumours transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

5.2 Pharmacokinetic properties

In patients with normal hepatic and renal function, epirubicin hydrochloride plasma levels after intravenous administration of 60-150 mg/m² 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 hydrochloride and epirubicinol.

The 4'-O-glucuronidation distinguishes epirubicin hydrochloride from doxorubicin and may account for the faster elimination of epirubicin hydrochloride and its reduced toxicity. The plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel those of the unchanged drug.

Epirubicin hydrochloride is eliminated mainly through the liver; high plasma clearance levels (0.9 l/min) show that the 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.

5.3 Preclinical safety data

The main target organs in rat, rabbit and dog following repeated dosing were the haemolymphopoietic system, GI tract, kidney, liver and reproductive organs.

Epirubicin hydrochloride was also cardiotoxic in the species tested.

It was genotoxic, and, like other anthracyclines, carcinogenic in rats.

Epirubicin hydrochloride was embryotoxic in rats. No malformations were seen in rats or rabbits, but like other anthracyclines and cytotoxic drugs, epirubicin hydrochloride must be considered potentially teratogenic.

A local tolerance study in rats and mice showed extravasation of epirubicin hydrochloride causes tissue necrosis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Hydrochloric acid (For pH adjustment)

Water for Injections

6.2 Incompatibilities

Epirubicin hydrochloride contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug.

Epirubicin hydrochloride should not be mixed with heparin due to chemical incompatibility which may lead to precipitation when the drugs are in certain proportions.

Epirubicin hydrochloride can be used in combination with other antitumour agents, but it is not recommended that it be mixed with other drugs.

6.3 Shelf life

Shelf life of the product as package for sale:

2 year.

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.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C). Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage after dilution, see section 6.3.

6.5 Nature and contents of container

5 and 10 ml vials: Type I tubular glass vial with 20 mm chlorobutyl RTS rubber stopper and aluminium flip-off white seal.

25 ml vial: Type I tubular glass vial with 20 mm chlorobutyl RTS rubber stopper and aluminium flip-off white / royal blue seal.

50 ml vial: Type I clear moulded glass vial with 20 mm chlorobutyl RTS rubber stopper and aluminium flip-off royal blue seal.

100 ml vial: Type I clear moulded glass vial with 20 mm chlorobutyl RTS rubber stopper and aluminium flip-off white / royal blue seal.

Pack size: 1 vial.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Epirubicin Hydrochloride 2 mg/ml Injection may be further diluted in Glucose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. For information on the stability of the infusion solutions, please refer to section 6.3.

The solution for injection or infusion contains no preservative and any unused portion of the vial should be discarded immediately in accordance with local requirements.

Guidelines for the safe handling and disposal of antineoplastic agents:

1. If an infusion solution is to be prepared, this should be performed by trained personnel under aseptic conditions.
2. Preparation of an infusion solution should be performed in a designated aseptic area.
3. Adequate protective disposable gloves, goggles, gown and mask should be worn.
4. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In the event of contact with the eyes, irrigate with large amounts of water and/or 0.9% sodium chloride solution. Then seek medical evaluation by a physician.
5. 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. Always wash hands after removing gloves.
6. 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 detailed below.
7. Pregnant staff should not handle the cytotoxic preparation.
8. Adequate care and precautions should be taken in the disposal of items (syringes, needles etc) used to reconstitute and/or dilute cytotoxic medicinal products. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/034/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th March 2009

Date of last renewal: 11th January 2014

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