

SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Epirubicin Sandoz 2 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each milliliter (ml) of solution contains 2 mg of epirubicin hydrochloride.

1 vial of 5 ml solution contains 10 mg epirubicin hydrochloride.

1 vial of 25 ml solution contains 50 mg epirubicin hydrochloride.

1 vial of 50 ml solution contains 100 mg epirubicin hydrochloride.

1 vial of 100 ml solution contains 200 mg epirubicin hydrochloride.

The medicinal product contains 0.154 mmol/ml (3.54 mg/ml) sodium.

1 vial of 5 ml solution contains 0.77 mmol (17.70 mg) sodium.

1 vial of 25 ml solution contains 3.85 mmol (88.52 mg) sodium.

1 vial of 50 ml solution contains 7.70 mmol (177.02 mg) sodium.

1 vial of 100 ml solution contains 15.40 mmol (354.05 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection and infusion

Product description: 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

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
- Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection.

4.2 Posology and method of administration

Epirubicin Sandoz is for intravenous or intravesical use only.

The safety and efficacy of Epirubicin Sandoz in children has not been established.

Intravenous administration

It is advisable to administer Epirubicin Sandoz 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

When epirubicin hydrochloride is used as a single agent, the recommended dosage in adults is 60-90 mg/m² body area. Epirubicin hydrochloride should be injected intravenously over 3-5 minutes. The dose should be repeated at 21-day intervals, depending upon the patient's haematological status and bone marrow function.

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

For high dose treatment, epirubicin hydrochloride may be given as an intravenous bolus over 3-5 minutes or as an infusion of up to 30 minutes duration.

1.1 Breast Cancer

In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin hydrochloride ranging from 100 mg/m² (as a single dose on day 1) to 120 mg/m² (in two divided doses on days 1 and 8) every 3-4 weeks, in combination with intravenous cyclophosphamide and 5- fluorouracil and oral tamoxifen, are recommended.

Lower doses (60-75 mg/m² for conventional treatment and 105-120 mg/m² for high dose treatment) are recommended for patients whose bone marrow function has been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone marrow infiltration. The total dose per cycle may be divided over 2-3 successive days.

Doses for intravenous administration:

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

Cancer Indication	Epirubicin hydrochloride Dose (mg/m²)^a	
	Monotherapy	Combination Therapy
Gastric cancer	60–90	50

^{a)} Doses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals

Combination therapy

If Epirubicin Sandoz is used in combination with other cytotoxic products, the dose should be reduced accordingly. Commonly used doses are shown in the table above.

In establishing the maximal cumulative doses of epirubicin hydrochloride (usually: 720 – 1000 mg/m²), any concomitant therapy with potentially cardiotoxic drugs should be taken into account.

1.2 Impaired liver function

The major route of elimination of epirubicin hydrochloride is the hepatobiliary system. In patients with impaired liver function the dose should be reduced based on serum bilirubin levels as follows:

Serum Bilirubin	Dose Reduction
24 - 51 $\mu\text{mol/l}$	50%
> 51 $\mu\text{mol/l}$	75%

1.3 Impaired renal function

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin hydrochloride excreted by this route. However, dosage adjustment may be necessary in patients with serum creatinine >5 mg/dL.

1.4 Intravesical administration

Epirubicin hydrochloride can be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be given intravesically for the treatment of invasive tumours that have penetrated the bladder wall, systemic therapy or surgery is more appropriate in these situations (see Section 4.3). Epirubicin hydrochloride has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours to prevent recurrence.

Doses for intravesical administration:

The following doses of epirubicin hydrochloride are commonly used in monotherapy for bladder cancer:

	Monotherapy
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

For the treatment of superficial bladder cancer the following regimen is recommended, using the dilution table below:

8 weekly instillations of 50 mg/50 ml (diluted with saline or distilled sterile water).

If local toxicity is observed: A dose reduction to 30 mg/50 ml is advised.

Carcinoma-in-situ of the bladder: Up to 80 mg/50 ml (depending on individual tolerability of the patient)

For prophylaxis: 4 weekly administrations of 50 mg/50 ml followed by 11 monthly instillations at the same dose.

2 DILUTION TABLE FOR BLADDER INSTILLATION SOLUTIONS

Dose Epirubicin hydrochloride required	Volume of Epirubicin Sandoz 2 mg/ml	Volume of diluent sterile water for injection or 0.9% sterile	Total volume for bladder installation
--	-------------------------------------	---	---------------------------------------

	solution for injection	saline	
30 mg	15 ml	35 ml	50 ml
50 mg	25 ml	25 ml	50 ml
80 mg	40 ml	10 ml	50 ml

The solution should be retained intravesically for 1-2 hours. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. During the instillation, the patient should be rotated occasionally and should be instructed to void urine at the end of the instillation time.

4.3 Contraindications

- Hypersensitivity to epirubicin or any other component of the product, other anthracyclines or antracenediones.
- Lactation

Intravenous use

- Persistent myelosuppression myocardiopathy
- Previous treatments with maximal cumulative doses of epirubicin hydrochloride and/or other anthracyclines and antracenediones (see section 4.4)
- Recent myocardial infarction Severe arrhythmias
- Patients with acute systemic infections
- Sever hepatic impairment
- Unstable angina pectoris
- Severe mucositis of the mouth, pharynx, oesophagus, and gastro-intestinal tract.

Intravesical use

- Urinary tract infections
- Inflammation of the bladder
- Hematuria
- Invasive tumours penetrating the bladder
- Catheterisation problems
- Vesical inflammation
- Large volume of residual urine
- Contracted bladder.

4.4 Special warnings and precautions for use

General

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

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

While treatment with high doses of epirubicin hydrochloride (e.g. ≥ 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 hydrochloride 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 (i.e. acute) or late (i.e. delayed) events.

Early (i.e. 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 (i.e. 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 dyspnea, pulmonary edema, dependent edema, 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 hydrochloride in excess of 900 mg/m²; this cumulative dose should only be exceeded with extreme caution. (see section 5.1)

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 hydrochloride 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, concomitant use of other drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g. trastuzumab) (see section 4.5 Interaction with other medicinal products and other forms of interaction) with an increased risk in the elderly.

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

Trastuzumab and anthracyclines such as epirubicin should not be used currently in combination except in a well-controlled clinical trial setting with cardiac monitoring. Patients who have previously received anthracyclines are also at risk of cardiotoxicity with trastuzumab treatment, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.

Because the half-life of trastuzumab is approximately 28-38 days, trastuzumab may persist in the circulation for up to 27 weeks after stopping trastuzumab treatment. Patients who receive anthracyclines such as epirubicin after stopping trastuzumab may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab. If anthracyclines such as epirubicin are used, the patient's cardiac function should be monitored carefully.

If symptomatic cardiac failure develops during trastuzumab therapy after epirubicin therapy, it should be treated with the standard medications for this purpose

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.

Hematologic toxicity

As with other cytotoxic agents, epirubicin may produce myelosuppression. Hematologic 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 hematologic 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 anemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia or death.

Secondary leukemia

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

Gastrointestinal

Epirubicin is emetigenic. 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 and 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 section 4.2 Posology and administration). Patients with severe hepatic impairment should not receive epirubicin (see section 4.3 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 section 4.2 Posology and method of administration).

Effects at site of injection

Phleboscrosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see section 4.2 Posology and method of administration).

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 discontinued. The adverse effect of extravasation of anthracyclines may be prevented or reduced by immediate use of a specific treatment e.g. dexrazoxane (please refer to relevant labels for use). The patient's pain may be relieved by cooling down the area and keeping it cool, use of hyaluronic acid and DMSO. The patient should be monitored closely during the

subsequent period of time, as necrosis may occur after several weeks. If extravasation occurs, a plastic surgeon should be consulted with a view to possible excision.

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.

Tumor-lysis syndrome

Epirubicin may induce hyperuricemia because of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells (tumor-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate and creatinine should be evaluated after initial treatment. Hydration, urine alkalization and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-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 (see section 4.5 Interaction with other medicinal products and other forms of interactions). 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.

Reproductive systemEpirubicin can cause genotoxicity. Men and women treated with epirubicin should adopt appropriate contraceptives. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available.

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, hematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterization problems (e.g. urethral obstruction due to massive intravesical tumors).

Intra-arterial route

Intra-arterial administration of epirubicin (transcatheter arterial embolization 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) 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.

4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/hematologic and gastro-intestinal effects (see section 4.4 Special warnings and precautions for use).

The use of epirubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), requires monitoring of cardiac function throughout treatment.

Epirubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity (see section 4.4 Special warnings and precautions for use).

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.

Because the half-life of trastuzumab is approximately 28-38 days, trastuzumab may persist in the circulation for up to 27 weeks after stopping trastuzumab treatment. Patients who receive anthracyclines such as epirubicin hydrochloride after stopping trastuzumab may possibly be at an increased risk of cardio toxicity. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab. If anthracyclines such as epirubicin hydrochloride are used, the patient's cardiac function should be monitored carefully.

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.

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

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

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

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

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

Quinine may accelerate the initial distribution of epirubicin from blood into the tissues and may have an influence on the red blood cells partitioning of epirubicin.

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

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

Increase of myelosuppression may occur in patients receiving combination therapy of anthracycline and dexrazoxane.

4.6 Fertility, pregnancy and lactation

Impairment of Fertility

Epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should use effective contraceptive methods and if appropriate and available, seek advice on sperm preservation due to the possibility of irreversible infertility caused by therapy.

Epirubicin may cause amenorrhea or premature menopause in premenopausal women.

Pregnancy

Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and should use effective contraceptive methods.

Experimental data in animals suggest that epirubicin may cause foetal harm when administered to a pregnant woman. If epirubicin 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 in pregnant women. Epirubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding

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, 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 the effects on ability to drive and to use machines.

Epirubicin may cause episodes of nausea and vomiting, which can temporarily lead to an impairment of ability to drive or operate machines.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with epirubicin with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data)

More than 10% of treated patients can expect to develop undesirable effects. The most common undesirable effects are myelosuppression, gastrointestinal side effects, anorexia, alopecia, infection.

System organ class	Frequency	Undesirable effects
Infections and infestations	Common	Infection
	Not known	Septic shock, sepsis, pneumonia
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Rare	Acute lymphocytic leukaemia, acute myelogenous leukaemia
Blood and the lymphatic system disorders	Very common	Myelosuppression (leukopenia, granulocytopenia and neutropenia, anaemia and febrile neutropenia)
	Uncommon	Thrombocytopenia
	Not known	Haemorrhage and tissue hypoxia as result of myelosuppression
Immune system disorders	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common	Anorexia, dehydration
	Rare	Hyperuricemia (see section 4.4)
Nervous system disorders	Rare	Dizziness
Eye disorders	Not known	Conjunctivitis, keratitis
Cardiac disorders	Rare	Congestive heart failure, (dyspnoea; oedema, hepatomegaly, ascites, pulmonary oedema, pleural effusions, gallop rhythm) cardiotoxicity (e.g. ECG abnormalities, arrhythmias, cardiomyopathy), ventricular tachycardia, bradycardia, AV block, bundle-branch block
Vascular disorders	Common	Hot flashes
	Uncommon	Phlebitis, thrombophlebitis
	Not known	Shock, thromboembolism, including pulmonary emboli
Gastrointestinal disorders	Common	Mucositis, esophagitis, stomatitis, vomiting, diarrhoea, nausea

	Not known	Oral mucosa erosion, mouth ulceration, oral pain, mucosal burning sensation, mouth haemorrhage, and buccal pigmentation
Skin and subcutaneous tissue disorders	Very common	Alopecia
	Rare	Urticaria
	Not known	Local toxicity, rash, itch, skin changes, erythema, flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction)
Renal and urinary disorders	Very common	Red coloration of urine for 1 to 2 days after administration
Reproductive system and breast disorders	Rare	Amenorrhea, azoospermia
General disorders and administration site conditions	Common	Infusion site erythema
	Rare	Malaise, asthenia, fever, chills
	Not known	Phlebosclerosis, local pain, severe cellulitis, tissue necrosis after accidental paravenous injection
Investigations	Rare	Changes in transaminase levels
	Not Known	Asymptomatic drops in left ventricular ejection fraction
Injury, poisoning and procedural complications	Common	Chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration (see section 4.4)

Intravesical administration

As only a small amount of active ingredient is reabsorbed after intravesical instillation, severe systemic adverse drug reactions as well as allergic reactions are rare. Commonly reported are local reactions like burning sensation and frequent voiding (pollakisuria). Occasional bacterial or chemical cystitis have been reported (see section 4.4 Special warnings and precautions for use). These ADRs are mostly reversible.

4.9 Overdose

Acute overdosage with epirubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications. Latent cardiac failure has been observed with anthracyclines several months to years after completion of treatment (see section 4.4 Special warnings and precautions for use). Patients must be carefully

monitored. If signs of cardiac failure occur, patients should be treated according to conventional guidelines.

Treatment

Symptomatic; Epirubicin cannot be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent. ATC code: L01D B03

Epirubicin is a cytotoxic active antibiotic from the anthracycline group. 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 tumours 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 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, plasma levels after intravenous injection of 60-150 mg/m² 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. Between 60 and 120 mg/m² there is an extensive linear pharmacokinetic, 150 mg/m² is at the margin of dose linearity. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.

In pharmacokinetic studies of patients with carcinoma in situ of the bladder the plasma levels of epirubicin after intravesical instillation are typically low (<10 ng/ml). a significant systemic resorption can therefore not be assumed. In patients with lesions of the mucosa of the bladder (e.g. tumour, cystitis, operations), a higher resorption rate can be expected.

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.

5.3 Preclinical safety data

Following repeated dosing with epirubicin, the target organs in rat, rabbit and dog were the haemolymphopoietic system, GI tract, kidney, liver and reproductive organs. Epirubicin was also cardiotoxic in the rat, rabbit and dog.

Epirubicin, like other anthracyclines, was mutagenic, genotoxic, embryotoxic and carcinogenic in rats.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,

hydrochloric acid (for pH adjustment),

water for injections.

6.2 Incompatibilities

Prolonged contact of the medicinal product with any solution of an alkaline pH should be avoided: this will result in hydrolysis (degradation) of the active substance. A physical incompatibility of the product with heparin has been reported. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf-life

Medicinal product as packaged for sale: 2 years

Shelf life after dilution:

Chemical and physical in-use stability has been demonstrated for 7 days at 2 to 8°C in Glucose 5 % or Sodium Chloride 0.9 %.

In use: 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 normally not be longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Store refrigerated (2°C to 8°C). For storage conditions after dilution of the medicinal product, see section 6.3.

Storage of the 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 2 to a maximum of 4 hours equilibration at controlled room temperature (15° to 25°C).

6.5 Nature and contents of container

Type 1 glass vials with a rubber (chlorobutyl) stopper with/without a protective plastic overwrap (ONKO-SAFE).

Packs of

1 vial, 5 or 10 vials containing 5 ml of solution.

1 vial, 5 or 10 vials containing 25 ml of solution.

1 vial, 5 or 10 vials containing 50 ml of solution.

1 vial, 5 or 10 vials containing 100 ml of solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Epirubicin Hydrochloride 2 mg/ml Injection may be further diluted in Glucose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. The infusion solution should be prepared immediately before use.

For instructions on the administration of the product, see section 4.2.

The injection solution contains no preservative and any unused portion of the vial should be discarded immediately.

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 AUTHORIZATION HOLDER

Sandoz GmbH

8. MARKETING AUTHORISATION NUMBER(S)

04897/06815/REN/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

January 6, 2020

10. DATE OF REVISION OF THE TEXT

May-2016