SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin Hydrochloride 50 mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of epirubicin hydrochloride
After reconstitution, each vial contains 2 mg/ml epirubicin hydrochloride

Excipient with known effect
Each 50 mg vial contains 10 mg of methyl hydroxybenzoate.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection

A sterile freeze dried orange red coloured lyophilised cake.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epirubicin hydrochloride has produced responses in a wide range of neoplastic conditions, including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphomas, leukaemias and multiple myeloma.
Intravesical administration of Epirubicin hydrochloride has been found to be beneficial in the treatment of superficial bladder cancer, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection.

4.2 Posology and method of administration

Posology

Epirubicin hydrochloride is not active when given orally and should not be injected intramuscularly or intrathecally.

Preparation of the freeze-dried powder

The product should be dissolved in 5 ml 0.9% sodium chloride or water for injections to get the final concentration of 2 mg/ml. The vial contents will be under a negative pressure. To minimize aerosol formation during reconstitution, particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided. After gentle agitation the reconstituted solution will be transparent and red in appearance.

Intravenous administration:

It is advisable to give the drug via the tubing of a freely-running IV saline infusion after checking that the needle is well placed in the vein. This method minimises the risk of drug extravasation and makes sure that the vein is flushed with saline after the administration of the drug. Extravasation of Epirubicin hydrochloride from the vein during injection may give rise to severe tissue lesions, even necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Conventional doses:

When Epirubicin hydrochloride is used as a single agent, the recommended dosage in adults is 60-90 mg/m^2 body area; the drug should be injected I.V. over 3-5 minutes and, depending upon the patients' haematological status the dose should be repeated at 21-day intervals.

High doses

Epirubicin hydrochloride as a single agent for the treatment of lung cancer at high doses should be administered according to the following regimens:

Lung cancer

- Small cell lung cancer (previously untreated): 120 mg/m^2 day 1, every 3 weeks.
- Non-small cell lung cancer (squamous, large cell, and adenocarcinoma previously untreated): 135 mg/m^2 day 1 or 45 mg/m^2 days 1, 2, 3, every 3 weeks.

Breast cancer

In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of Epirubicin hydrochloride ranging from 100 mg/m^2 (as a single dose on day 1) to 120 mg/m^2 (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.

The drug should be given as an I.V. bolus over 3-5 minutes or as an infusion up to 30 minutes. Lower doses (60-75 mg/ m^2 for conventional treatment and 105-120 mg/ m^2 for high dose schedules) are recommended for patients whose bone marrow function has already 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.

When the drug is used in combination with other antitumour agents, the doses need to be adequately reduced.

Since the major route of elimination of Epirubicin hydrochloride is the hepatobiliary system, the dosage should be reduced in patients with impaired liver function, in order to avoid an increase in overall toxicity. Moderate liver impairment (bilirubin: 1.4 - 3 mg/100 ml) requires a 50% reduction of dose, while severe impairment (bilirubin > 3mg/100 ml) necessitates a dose reduction of 75%.

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Epirubicin hydrochloride excreted by this route.

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 used in this way for the treatment of invasive tumours which have penetrated the bladder wall where systemic therapy or surgery is more appropriate. Epirubicin hydrochloride has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours in order to prevent recurrences.

While many regimens have been used, the following may be helpful as a guide: for therapy, 8 x weekly instillations of 50 mg/50 ml (diluted with saline or distilled sterile water). In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg/50ml is advised. For carcinoma-in-situ, depending on the individual tolerability of the patient, the dose may be increased up to 80 mg/50 ml. For prophylaxis, 4 x weekly administrations of 50 mg/50 ml, followed by 11 x monthly instillations at the same dosage, is the schedule most commonly used.

The solution should be retained intravesically for 1 hour. 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 at the end of the instillation time.

4.3 Contraindications

Hypersensitivity to epirubicin or to any of the excipients listed in section 6.1, other anthracyclines or anthracenediones.

- Lactation

Intravenous use:

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

Intravesical use:

- urinary tract infections
- inflammation of the bladder
- haematuria
- invasive tumours penetrating the bladder
- catheterisation problems

4.4 Special warnings and precautions for use

General

Epirubicin hydrochloride 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 generalised infections) of prior cytotoxic treatment before beginning treatment with Epirubicin hydrochloride.

While treatment with high doses of Epirubicin hydrochloride (e.g. $\geq$ 90 mg/m^2 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/mucosal inflammation 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 hydrochloride 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

n for the discontinuation of Epirubicin hydrochloride treatment.

Late (i.e. Delayed) Events - Delayed cardiotoxicity usually develops late in the course of therapy with Epirubicin hydrochloride 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,

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 hydrochloride and must be monitored throughout therapy to minimise 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 hydrochloride 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) 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 hydrochloride. This may be moderate to severe and has been associated with death.
Trastuzumab and anthracyclines such as Epirubicin hydrochloride should not be used currently in combination except in a well-controlled clinical trial

setting with cardiac monitoring. Patients who have previously received

o at risk of cardiotoxicity with trastuzumab treatment, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.

The reported half-life of trastuzumab is variable. The substance may persist in the circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If this is not possible, the patient's cardiac function should be monitored carefully.

If symptomatic cardiac failure develops during trastuzumab therapy after Epirubicin hydrochloride 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 hydrochloride may occur at lower cumulative doses whether or not cardiac risk factors are present.

There have been sporadic reports of foetal/neonatal cardiotoxic events including foetal death following in utero exposure to Epirubicin hydrochloride (see section 4.6).

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

Haematological toxicity - As with other cytotoxic agents, Epirubicin hydrochloride may produce myelosuppression. Haematologic profiles should be assessed before and during each cycle of therapy with Epirubicin hydrochloride, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of Epirubicin hydrochloride 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 pyrexia, infection, sepsis/septicaemia, septic shock, haemorrhage, tissues hypoxia, or death.

Secondary Leukaemia - Secondary leukaemia, with or without a preleukaemic phase, has been reported in patients treated with anthracyclines, including Epirubicin hydrochloride. Secondary leukaemia 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 leukaemias can have a 1 to 3-year latency period (see section 5.1).

Gastrointestinal - Epirubicin hydrochloride is emetogenic. Mucosal inflammation/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 hydrochloride is the hepatobiliary system. Serum total bilirubin and AST levels should be evaluated before and during treatment with Epirubicin hydrochloride. Patients with elevated bilirubin or AST may experience slower clearance of the drug with an increase in overall toxicity. Lower doses are recommended in these patients (see sections 4.2 and 5.2). Patients with severe hepatic impairment should not receive Epirubicin hydrochloride (see section 4.3).

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).

Effects at site of injection - Phlebosclerosis may result from an 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 section 4.2).

Extravasation

Extravasation of Epirubicin hydrochloride 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 hydrochloride, 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 using 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 hydrochloride.

Tumour-lysis syndrome - Epirubicin hydrochloride may induce hyperuricaemia because of the extensive purine catabolism that accompanies 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

hydrochloride, may result in serious or fatal infections (see section 4.5). Vaccination with a live vaccine should be avoided in patients receiving Epirubicin hydrochloride. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Reproductive system - Epirubicin hydrochloride can cause genotoxicity. Men and women treated with Epirubicin hydrochloride should adopt appropriate contraceptives during and for a period after treatment with Epirubicin hydrochloride (see section 4.6). 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 hydrochloride 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., ureteral obstruction due to massive intravesical tumours).

Intra-arterial route - Intra-arterial administration of Epirubicin hydrochloride (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 hydrochloride) 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.

Excipients with known effect
This medicinal product may be further prepared for administration with sodium containing solutions (see section 4.2 and section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

Epirubicin hydrochloride, powder for solution for injection, contains methyl hydroxybenzoate. This may cause allergic reactions (which may occur after treatment), and in rare cases, respiratory difficulties.

4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin hydrochloride is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone

marrow/haematologic and gastro-intestinal effects (see section 4.4). The use of Epirubicin hydrochloride 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 hydrochloride is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect Epirubicin hydrochloride metabolism, pharmacokinetics, therapeutic efficacy and/ or toxicity (see section 4.4).

Anthracyclines including epirubicin hydrochloride 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 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

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. Co-administration 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 may accelerate the initial distribution of Epirubicin hydrochloride from blood into the tissues and may have an influence on the red blood cells partitioning of Epirubicin hydrochloride.

The co-administration of interferon α_{2b} may cause a reduction in both the terminal elimination half-life and the total 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 influences the bone

marrow (i.e. cytostatic agents, sulphonamide, chloramphenicol, diphenylhydantoin, amidopyrine-derivatives, antiretroviral agents).

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

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no studies in pregnant women. Experimental data in animals suggest that Epirubicin hydrochloride may cause foetal harm when administered to a pregnant woman, particularly in the first trimester.

If Epirubicin hydrochloride is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the foetus. There have been sporadic reports of foetal and/or neonatal transient ventricular hypokinesia, transient elevation of cardiac enzymes, and of foetal death from suspected anthracycline-induced cardiotoxicity following in utero exposure to Epirubicin hydrochloride in 2nd and/or 3rd trimesters (see section 4.4). Monitor the foetus and/or neonate for cardiotoxicity and perform testing consistent with community standards of care.

Epirubicin hydrochloride should be used during pregnancy only if the potential benefit justifies the risk to the foetus.

Breast-feeding

It is not known whether Epirubicin hydrochloride 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 hydrochloride, lactating women should be advised not to breastfeed during treatment with Epirubicin hydrochloride and for at least 7 days after the last dose.

Fertility

Epirubicin hydrochloride could induce chromosomal damage in human spermatozoa. Men undergoing treatment with Epirubicin hydrochloride are advised not to father a child during treatment and to seek advice regarding cryopreservation of sperm prior to treatment due to the possibility of irreversible infertility caused by therapy, and/or to use individual genetic counselling for male or female patients intending to have a child after treatment with Epirubicin hydrochloride.

Males

The recommended duration of conception in male patients should be until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 90 days. The same would be true for a pure aneugenic compound.

Implications for Clinical trial applications

For male patients in clinical trials the recommendation for use of effective contraceptive measures after cessation of treatment with a genotoxic or aneugenic compound should be the following:

"Use of a condom plus an additional contraceptive method that together result in a failure rate of <1% per year to avoid conception during treatment and until the end of relevant systemic exposure in the exposed male or for five terminal half-lives plus 90 days (life span of spermatozoa of 60-75 days for sperm production + 10-14 days for transport to epididymis)." (Banholzer et al., 2016, [3]).

Females

It takes approximately 6 months for an oocyte to mature from the primordial to the Graafian stage. Animal studies have demonstrated that oocytes exposed to a genotoxic compound at the earliest stage of maturation led to an increase in foetal malformation in pregnancies, whilst exposure of oocytes at the pre-ovulatory stage entailed the highest abortion rate.

Implications for Clinical trial applications

The recommended duration of contraception in female subjects participating in clinical trials should be until the end of relevant systemic exposure including potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 6 months. In the more theoretical case of treatment with a pure aneugenic pharmaceutical recommended duration of contraception should be until the end of relevant systemic exposure (i.e. five half-lives after the last dose) plus 1 month.

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

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 undesirable effects have been observed and reported during treatment with Epirubicin hydrochloride with the following frequencies: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (frequency cannot be estimated form the available data).

System Organ Class	Frequency	Undesirable effects
Infections and infestations	Very common	Infection, conjunctivitis
	Uncommon	Sepsis*, pneumonia*
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Uncommon	Acute lymphocytic leukaemia, acute myeloid leukaemia
Blood and lymphatic system disorders	Very common	Leukopenia, neutropenia, anaemia, febrile neutropenia, thrombocytopenia
Immune system disorders	Rare	Anaphylactic reactions*
Metabolism and nutrition disorders	Common	Decreased appetite, dehydration*
	Rare	Hyperuricemia*
Eye disorders	Very common	Keratitis
Cardiac disorders	Common	Ventricular tachycardia, atrioventricular block, bundle-branch block, bradycardia, cardiac failure congestive
Vascular disorders	Very common	Hot flush, phlebitis*
	Common	Haemorrhage*, flushing*
	Uncommon	Embolism, embolism arterial*, thrombophlebitis*

	Not known	Shock*
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary embolism*
Gastrointestinal disorders	Very common	Mucosal inflammation, stomatitis, vomiting, diarrhoea, nausea
	Common	Gastrointestinal pain*, gastrointestinal erosion*, gastrointestinal ulcer*
	Uncommon	G haemorrhage*
	Not known	Abdominal discomfort, pigmentation buccal*
Skin and subcutaneous tissue disorders	Very common	Alopecia, skin toxicity
	Common	Rash/pruritus, nail pigmentation*, skin disorder, skin hyperpigmentation*
	Uncommon	Urticaria*, erythema*
	Not known	Photosensitivity reaction*
Renal and urinary disorders	Very common	Chromaturia*†
Reproductive system and breast disorders	Very common	Amenorrhoea
General disorders and administration site conditions	Very common	Malaise, pyrexia*
	Common	Chills*
	Uncommon	Asthenia
Investigations	Very common	Transaminases abnormal
	Common	Ejection fraction decreased
Injury, poisoning and procedural complications	Very common	Chemical cystitis*§
	Not known	Recall phenomenon*Δ

***** ADR identified post-marketing.
† Red colouration of urine for 1 to 2 days after administration.
§ Following intravesical administration.
Δ Hypersensitivity to irradiated skin (radiation recall reaction).

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 www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdosage with Epirubicin hydrochloride will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucosal inflammation) and acute cardiac complications. Latent cardiac failure has been observed with anthracyclines several months to years after completion of treatment (see section 4.4). Patients must be carefully monitored. If signs of cardiac failure occur, patients should be treated according to conventional guidelines.

Treatment

Symptomatic.

Epirubicin hydrochloride cannot be removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthracyclines and related substances, ATC code: L01DB03

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, 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 I.V. injection of 60-150mg/m^2 of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. Between 60 and 120 mg/m^2 there is an extensive linear pharmacokinetic, 150 mg/m^2 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.

The 4'-O-glucuronidation distinguishes Epirubicin hydrochloride from doxorubicin and may account for the faster elimination of Epirubicin hydrochloride 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 hydrochloride 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

The main target organs of toxicity following administration of Epirubicin hydrochloride to animals were the haemolymphopoietic system, GI tract, heart, kidney, liver and reproductive organs.

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

Epirubicin hydrochloride, was toxic to male and female reproductive organs in animal studies. In male rats, administration of Epirubicin hydrochloride caused decreases in size/weight of the testes and/or epididymides, and reduced spermatogenesis. In females, Epirubicin hydrochloride caused gross alterations in the ovaries and uteri in rats and uterine atrophy in rats and dogs.

Epirubicin hydrochloride was embryotoxic and teratogenic when administered during the period of organogenesis in pregnant rats, with an increased incidence of visceral abnormalities observed. No malformations were observed in 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 hydrochloride causes tissue necrosis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl hydroxybenzoate (E218),

Lactose monohydrate,

Hydrochloric acid,

Water for injection.

6.2 Incompatibilities

Prolonged contact of the medicinal product with any solution of an alkaline pH (including sodium bicarbonate solutions) should be avoided; this will result in hydrolysis (degradation) of the active substance. Only the diluents detailed in section 6.3 should be used.

A physical incompatibility of the medicinal 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

Shelf life of the product as packaged for sale: 2 years

Shelf life after reconstitution according to directions:

In-use stability has been demonstrated for 24 hours at 15°C - 25°C and for 48 hours at 2 - 8°C in water for injections and 0.9% w/v sodium chloride solution. However from a microbiological point of view, it is recommended that 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 8ºC.'

6.4 Special precautions for storage

Store below 30°C.

Keep the vial in the outer carton.

For storage conditions of the reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container

Epirubicin hydrochloride 50 mg is produced in 50 ml Type I moulded flint glass vial with 20 mm bromo butyl rubber stoppers and 20 mm aluminium flip-off tear-off seal.

1 vial per pack

6.6 Special precautions for disposal

Epirubicin hydrochloride may be further diluted in glucose 5% solution or sodium chloride 0.9% solution and administered as an intravenous infusion. For information on the stability of the infusion solutions please refer to section 6.3.

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

Guidelines for the safe handling and disposal of antineoplastic agents:

- If an infusion solution is to be prepared, this should be performed by trained personnel under aseptic conditions.
- Preparation of an infusion solution should be performed in a designated aseptic area.
- Adequate protective disposable gloves, goggles, gown and mask should be worn.
- 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.
- 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.

- 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.
- Pregnant staff should not handle the cytotoxic preparation.
- 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

Dawa Ltd
5 Sandridge Close, Harrow,
Middlesex, HA1 1XD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 30684/0142

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/01/2025

10 DATE OF REVISION OF THE TEXT

27/03/2025