NEW ZEALAND DATA SHEET
EPIRUBICIN EBEWE (EPIRUBICIN HYDROCHLORIDE)

1. PRODUCT NAME

Epirubicin Ebewe solution for injection 2 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active: Epirubicin hydrochloride

Each vial contains 2 mg/mL of epirubicin hydrochloride

Epirubicin hydrochloride is a red-orange, almost odourless, hygroscopic powder, sparingly soluble in water and dilute alcohol.

List of excipients with known effect: Sodium chloride

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection (clear red solution, vials).

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

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

In bladder cancer, epirubicin hydrochloride is also indicated in the prophylaxis of recurrence after transurethral resection of stage T1 papillary cancers and stage Ta multifocal papillary cancers (grade 2 and 3).

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

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

Care in the intravenous administration of epirubicin hydrochloride will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions, such as urticaria and erythematous streaking (see Section 4.4 Special warnings and precautions for use).

Note. The recommended lifetime cumulative dose limit of epirubicin is 900 mg/m^2 body surface area.

Under conditions of normal recovery from drug induced toxicity (particularly bone marrow depression and stomatitis), the recommended dosage schedule in adults, as described below, is as a single intravenous injection administered at 21 day intervals.

Standard doses are 75 to 90 mg/m^2. Epirubicin produces predominantly haematological dose limiting toxicities, which are predicted from the known dose response profile of the drug. Based on the patient's haematological status the doctor should determine the choice of dose.

Higher doses, up to 135 mg/m^2 as a single agent and 120 mg/m^2 in combination, every three to four weeks have been effective in the treatment of breast cancer. In the adjuvant treatment of early breast cancer patients with positive lymph nodes, doses ranging from 100 mg/m^2 to 120 mg/m^2 every three to four weeks are recommended. Careful monitoring in regards to increased myelosuppression, nausea, vomiting and mucositis are recommended in this high dose setting.

Consideration should be given to the administration of lower starting doses (not exceeding 75 to 90 mg/m^2) for heavily pretreated patients, patients with pre-existing bone marrow depression or in the presence of neoplastic bone marrow infiltration. If epirubicin hydrochloride is used in combination with other cytotoxic drugs with potentially overlapping toxicities, the recommended dose per cycle should be reduced accordingly.

Intravesical administration

For the treatment of papillary transitional cell carcinoma of the bladder, a therapy of eight weekly instillations of 50 mg is recommended.

In the case of local toxicity (chemical cystitis), a dose reduction up to 30 mg is advised. For carcinoma in situ, depending on the individual tolerability of the patient, the dose may be increased up to 80 mg.

For prophylaxis of recurrences after transurethral resection of superficial tumours, four weekly administrations of 50 mg followed by eleven monthly instillations at the same dosage are recommended.

To avoid undue dilution with the urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation.

Intravesical administration is not suitable for the treatment of invasive tumours, which have penetrated the muscular layer of the bladder wall.

The product does not contain a preservative. Use once only and discard any residue.

Method of administration

Epirubicin is intended for intravenous or intravesical administration only. It must not be administered by the intramuscular, subcutaneous or oral routes.

Intravenous administration

It is recommended that epirubicin hydrochloride be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection USP or 5% Glucose Injection USP. The tubing should be attached to a butterfly needle inserted preferably into a large vein. The rate of administration is dependent on the size of the vein and the dosage. However, the dosage should be administrated in not less than three to four minutes. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein (see Section 4.4 Special warnings and precautions for use).

Intravesical administration

The solution of epirubicin hydrochloride, to be instilled using a catheter, should be retained intravesically for one hour. The patient should be instructed to void at the end of this time. During instillation, the pelvis of the patient should be rotated to ensure extensive contact of the solution with the vesical mucosa.

Dosage adjustment in:

- renal impairment

While no specific dose recommendation can be made on the limited available data in patients with renal impairment, lower starting doses should be considered in patients with severe renal impairment (serum creatinine > 5 mg/dL).

- hepatic impairment

As clinical toxicity may be increased by the presence of impaired liver function, epirubicin hydrochloride dosage must be reduced if hepatic function is impaired, according to Table 1.

Table 1. Epirubicin – Dosage in hepatic impairment

Serum bilirubin levels	Recommended dose
20-50 µmol/L	½ normal dose
Over 50 µmol/L	¼ normal dose

- Other special populations

Haematological toxicity may require dose reduction, delay or suspension of epirubicin hydrochloride therapy. Lower doses may be necessary if epirubicin hydrochloride is used concurrently with other antineoplastic agents.

Compatibility

Epirubicin hydrochloride is compatible with the following infusion media: 0.9% sodium chloride, 5% glucose, 0.9% sodium chloride with 5% glucose.

Epirubicin hydrochloride can be used in combination with other antitumour agents.

4.3. CONTRAINDICATIONS

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

Intravenous use

Situations in which patients should not be treated with intravenous epirubicin hydrochloride are persisting myelosuppression or severe stomatitis induced by previous drug therapy or radiotherapy; presence of generalised infections; marked liver function impairment; previous history of, or in the presence of, cardiac impairment (severe arrhythmias and cardiomyopathy, previous myocardial infarction); previous treatments with maximum cumulative doses of mitozantrone, mitomycin C or other anthracyclines, such as doxorubicin or daunorubicin; pregnancy and lactation, unstable angina pectoris.

Intravesical use

Contraindications for intravesical use are:

- Invasive tumours that have penetrated the bladder wall
- Urinary infections
- Inflammation of the bladder
- Catheterisation problems
- Haematuria

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Epirubicin hydrochloride should be administered only under the supervision of qualified doctors experienced in 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 hydrochloride.

While treatment with high doses of epirubicin hydrochloride (e.g. greater than or equal to 90 mg/m^2 every three to four weeks) causes adverse events generally similar to those seen at standard doses (e.g. < 90 mg/m^2 every three to four weeks), the severity of neutropenia and stomatitis/ mucositis may be increased. In particular, treatment with high doses of the drug requires special attention for possible clinical complications due to profound myelosuppression.

Initial treatment with epirubicin hydrochloride requires close observation of the patient and extensive laboratory monitoring including assessment of cardiac function (see Section 4.4 Special warnings and precautions for use/ anthracycline induced cardiotoxicity). During each cycle of treatment, patients must be carefully and frequently monitored. A blood count, renal and liver function tests should be carried out prior to each epirubicin hydrochloride treatment. The routine assessment of cardiac function may include electrocardiogram (ECG) and the evaluation of left ventricular ejection fraction (LVEF).

Warnings

Epirubicin hydrochloride must be handled with care. If the preparation comes in contact with the skin or mucosae, the appropriate areas should be washed immediately and thoroughly with soap and water or sodium bicarbonate solution.

Epirubicin hydrochloride is intended for use under the direction of those experienced in cytotoxic therapy. The rate of administration is dependent on the size of the vein and the dosage. It is important that the dose be administered in not less than three to four minutes. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Severe local tissue necrosis will occur if there is extravasation during administration. Venous sclerosis may result from infection into a small vessel or from repeated injections into the same vein.

Epirubicin hydrochloride must not be given by the intramuscular or subcutaneous route.

Epirubicin hydrochloride is not an antimicrobial agent.

Haematological Toxicity

As with other cytotoxic agents, epirubicin may produce myelosuppression. Haematologic profiles should be assessed before and during each cycle of therapy with epirubicin including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopaenia and/or granulocytopaenia (neutorpaenia) is the predominant manifestation of epirubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopaenia and neutropaenia 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. Thrombocytopaenia and anaemia may also occur.

Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

Myelosuppression is more common in patients who have had extensive radiotherapy, bone marrow infiltration by tumour or impaired liver function (when appropriate dosage reduction has not been adopted) (see Section 4.2 Dose and method of administration – Dosage adjustment in, Other special populations).

Secondary Leukaemia

Secondary leukaemia, with or without a pre-leukaemic phase, has been reported in patients treated with anthracyclines including epirubicin. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily 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.

Anthracycline induced cardiotoxicity

Patients receiving epirubicin hydrochloride should be monitored for anthracycline induced cardiotoxicity, that may be manifested by early (i.e. acute) or late (i.e. delayed) events.

Heart function should be carefully monitored during treatment in order to minimise the risk of cardiac failure, of the type described for other anthracycline compounds.

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 waves changes. ECG changes following epirubicin hydrochloride treatment occur in about 10% of patients. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia, and bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These events 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 hydrochloride or within two or three months after treatment termination, but later events several months to years after completion of treatment have also been reported. Cardiomyopathy induced by anthracyclines is associated with persistent QRS voltage reduction, prolongation beyond normal limits of the systolic time interval (PEP/LVET) and a reduction of the ejection fraction and/or signs and symptoms of congestive heart failure (CHF) such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and

heptomegaly, 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. Pericardial effusion has also been described.

The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin in excess of 900 mg/m^2; this cumulative dose should only be exceeded with extreme caution.

Cardiac function should be assessed before patients undergo treatment with epirubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of left ventricular ejection fraction (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.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, concomitant or previous radiation of the mediastinal pericardial area, hypertensive cardiomyopathy, previous therapy with other anthracyclines/ anthracenediones, concomitant use of other drugs with the ability to suprpress cardiac contractility or cardiotoxic agents (e.g. trastuzumab, high dose cyclophosphamide or fluorouracil) with an increased risk in the elderly. Anthracyclines including epirubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The half-life of trastuzumab is approximately 28.5 days, however is variable and 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 anthracyclines are used before this time careful, monitoring of cardiac function is recommended.

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

There have been sporadic reports of fetal/neonatal cardiotoxic events including fetal death following *in utero* exposure to epirubicin (see Section 4.6 Fertility, pregnancy and lactation).

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

Gastrointestinal

Epirubicin is emetigentic. Nausea and vomiting may be prevented or alleviated by the administration of appropriate antiemetic therapy.

Mucositis/stomatitis occurs frequently and generally appears early after drug administration, most commonly developing 5 to 10 days after treatment. It is painful and typically begins as a burning sensation in the mouth and pharynx. The mucositis may involve the vagina, rectum and oesophagus, and, if severe, may progress over a few days to mucosal ulcerations with a

risk of secondary infection. Most patients recover from this adverse event by the third week of therapy.

Hepatoxicity

As toxicity of epirubicin hydrochloride is enhanced by impaired liver function or bile outflow, the major route of elimination being the hepatobiliary system, dosages should be reduced in patients with impaired hepatic function (see also Section 4.2 Dose and method of administration). Serum total bilirubin and AST levels should be evaluated before and during treatment with epirubicin hydrochloride. Patients with severe hepatic impairment should not receive epirubicin hydrochloride (see Section 4.3 Contraindications).

Effect 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 Dose and method of administration – Intravenous Administration).

Extravasation

Extravasation of epirubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. The recommended administration procedures should be followed (see Section 4.2 Dose and method of administration – Intravenous Administration). Should signs or symptoms of extravasation occur during intravenous administration of epirubicin, the drug infusion should be immediately stopped. 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 extravasation occurs, a plastic surgeon should be consulted with a view to possible excision.

Tumour-Lysis Syndrome

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

Embryo-fetal toxicity

Epirubicin can cause genotoxicity. An effective method of contraception is required for both male and female patients during and for a period after treatment with epirubicin (see Section

4.6 Fertility, pregnancy and lactation). Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available.

Other

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

Epirubicin hydrochloride may enhance radiation induced toxicity such as skin reactions and mucositis and may potentiate the toxicity of other anticancer therapies. This has to be taken into account particularly when using the drug in high doses and the availability of supportive care and facilities has to be considered before initiating high dose intensive regimens.

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

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., uretheral 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.

Use in renal impairment

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, serum creatinine should be assessed before and during therapy as dosage, adjustment is necessary in patients with serum creatinine > 5 mg/dL (see Section 4.2 Dose and method of administration).

Use in the elderly

No data available.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Epirubicin hydrochloride is mainly used in combination with other cytotoxic drugs and additive toxicity may occur especially with regard to bone marrow/ haematological and gastrointestinal

effects. In addition, the concomitant use of epirubicin hydrochloride with other antitumour drugs which have been reported as potentially cardiotoxic (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes, trastuzumab), as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), required a close monitoring of cardiac function throughout treatment.

Propranolol: concurrent administration of epirubicin hydrochloride and propranolol may result in an additive cardiotoxic effect.

Cimetidine increased the area under the curve (AUC) of epirubicin hydrochloride by 50% and should be stopped during the treatment with epirubicin hydrochloride.

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. Co-administration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin, 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 and paclitaxel should be performed with at least a 24-hour interval between the 2 agents.

Concurrent mediastinal radiotherapy and epirubicin hydrochloride may be associated with enhanced myocardial toxicity of epirubicin hydrochloride.

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

Cardiotoxic Medicines

Concurrent administration of epirubicin hydrochloride and cardiotoxic drugs such as propranolol and calcium channel blockers may precipitate congestive heart failure.

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 α2b 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

Effects on fertility

Studies in animals have shown reproductive toxicity. In fertility studies in rats, males were given epirubicin daily for 9 weeks and mated with females that were given epirubicin daily for 2 weeks prior to mating and through Day 7 of gestation. When 0.3 mg/kg/day (0.01-times the maximum recommended clinical dose based on body surface area, BSA) was administered to both sexes, no pregnancies resulted. No effects on mating behaviour or fertility were observed at 0.1 mg/kg/day, but male rats had atrophy of the testes and epididymis, and reduced spermatogenesis. Multiple daily doses of epirubicin to rabbits and dogs also caused atrophy of male reproductive organs. Single intravenous doses of epirubicin 20.5 and 12 mg/kg caused testicular atrophy in mice and rats, respectively. A single-dose of 16.7 mg/kg epirubicin caused uterine atrophy in rats.

In women, epirubicin hydrochloride may cause amenorrhoea. After termination of therapy, ovulation and menstruation may be expected to return in a few months, often accompanied by normal fertility. Premature menopause may occur.

In male patients, oligospermia or azoospermia may be permanent, although fertility may return several years after ceasing therapy. Given the mutagenic potential of epirubicin hydrochloride, the drug could induce chromosomal damage in human spermatozoa; therefore, males undergoing epirubicin hydrochloride treatment should be advised to use effective contraceptive methods during treatment and for at least 3.5 months after the last dose.

Based on animal studies, male and female fertility may be compromised. It is recommended to discuss fertility preservation with men and women prior to treatment.

Use in pregnancy

Category D

Category D – which have caused, are suspected to have cause or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and should use effective contraceptive methods during treatment and for at least 6.5 months after last dose.

There is no specific information available at present concerning the use of epirubicin hydrochloride in human pregnancy. However, as it has been shown to be embryotoxic and fetotoxic in animals, it should not be used in patients who are pregnant or are likely to become pregnant.

Administration of 0.8 mg/kg/day intravenously (0.04-times the maximum recommended clinical dose based on body surface area) of epirubicin to rats during days 5 to 15 of gestation was embryotoxic (increased resorptions and post-implantation loss) and caused fetal growth retardation (decreased body weight), but was not teratogenic up to this dose. Administration of 2 mg/kg/day intravenously (0.08-times the maximum recommended clinical dose based on body surface area) of epirubicin to rats on days 9 and 10 of gestation was embryotoxic (increased late resorptions, post-implantation losses, and dead fetuses; and decreased live fetuses), retarded fetal growth (decreased body weight), and caused decreased placental weight.

This dose was also teratogenic, causing numerous external (anal atresia, misshapen tail, abnormal genital tubercle), visceral (primarily gastrointestinal, urinary, and cardiovascular systems), and skeletal (deformed long bones and girdles, rib abnormalities, irregular spinal ossification) malformations. Administration of intravenous epirubicin to rabbits at doses up to 0.2 mg/kg/day (0.02-times the maximum recommended clinical dose based on body surface area) during days 6 to 18 of gestation was not embryotoxic or teratogenic, but a maternally toxic dose of 0.32 mg/kg/day increased abortions and delayed ossification. Administration of a maternally toxic intravenous dose of 1 mg/kg/day epirubicin (0.08-times the maximum recommended clinical dose based on body surface area) to rabbits on days 10 to 12 of gestation induced abortion, but no other signs of embryofetal toxicity or teratogenicity were observed. When doses up to 0.5 mg/kg/day epirubicin (0.02-times the maximum recommended clinical dose based on body surface area) were administered to rat dams from Day 17 of gestation to Day 21 after delivery, no permanent changes were observed in the development, functional activity, behaviour, or reproductive performance of the offspring.

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 fetus. There have been sporadic reports of fetal and/or neonatal transient ventricular hypokinesia, transient elevation of cardiac enzymes, and of fetal death from suspected anthracycline-induced cardiotoxicity following *in utero* exposure to epirubicin in 2nd and/or 3rd trimesters (see Section 4.4 Special warnings and precautions for use). Monitor the fetus and/or neonate for cardiotoxicity and perform testing consistent with community standards of care.

Use in lactation

In a peri- and post-natal study, epirubicin was present in milk of rats treated with 0.5 mg/kg/day epirubicin (0.02-times the maximum recommended clinical dose based on body surface area). It is likely that epirubicin is excreted in breast milk in humans, therefore, it is not recommended for nursing mothers unless the expected benefit outweighs any potential risk. Because of the potential for serious adverse reactions in nursing infants from epirubicin, lactating women should be advised not to breastfeed during treatment with epirubicin and for at least 7 days after last dose.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of epirubicin on the ability to drive or use machinery has not been systematically evaluated.

4.8. UNDESIRABLE EFFECTS

Dose limiting toxicities are myelosuppression and cardiotoxicity (described in detail under Precautions).

Adverse effects observed are:

More common reactions > 5%.

Haematological. Myelosuppression, leucopenia, granulocytopenia, neutropenia, thrombocytopenia, mild anaemia, secondary infection, febrile neutropenia.

Cardiovascular. Transient ECG changes, including low QRS voltage, tachycardia, arrhythmias, T wave flattening, ST depression and T inversion.

Gastrointestinal. Nausea, vomiting, diarrhoea and mucositis (erythema, erosions/ ulcerations, bleeding). Mucositis may appear five to ten days after the start of treatment and usually

involves stomatitis with areas of painful erosions, mainly along the sides of the tongue and on the sublingual mucosa.

Dermatological. Alopecia, including the interruption of beard growth, usually reversible, occurs in 60 to 90% of treated cases.

Application site. Erythematous streaking along the infused vein.

General. Dehydration.

Renal and Urinary Disorders. Red colouration of urine for 1 to 2 days after administration.

Less common reactions < 5%.

Haematological. Severe thrombocytopenia, anaemia, severe myelosuppression, pancytopenia, sepsis, septicaemia, septic shock, tissue hypoxia, haemorrhage and death.

Cardiovascular. Cardiomyopathy, congestive heart failure, cardiomegaly, atrioventricular and bundle branch block, tachyarrhythmias (premature ventricular contractions, ventricular tachycardia, bradycardia), asymptomatic drops in left ventricular ejection fraction.

Gastrointestinal. Oesophagitis, bleeding, hyperpigmentation of oral mucosa and abdominal pain or burning sensation.

Injury poisoning and procedural complications. Chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration

Dermatological. Local toxicity, rash/itch, skin changes, transient urticaria, erythema, flushes, skin and nail hyperpigmentation, photosensitivity and hypersensitivity of irradiated skin (radiation-recall reaction).

Application site. Vesication, phlebitis, thrombophlebitis and venous sclerosis. Local pain, severe cellulitis and skin necrosis following perivenous drug extravasation.

Neoplasms benign, malignant and unspecified (incl cysts and polyps). Acute lymphocytic leukemia, acute myelogenous leukemia.

Ocular. Conjunctivitis, keratitis.

Hepatic. Changes in transaminase levels.

Reproductive system and breast disorders. Amenorrhea, azoospermia

General. Chills and fever, anorexia, malaise/ asthenia, hot flushes. Anaphylaxis may occur.

Central Nervous System. Weakness, dizziness, confusion, depression, paraesthesia.

Vascular disorders. Hot flushes, phlebitis, thrombophlebitis, arterial embolism, shock, thromboembolism, including pulmonary emboli.

Metabolism and nutrition disorders. Anorexia, dehydration, hyperuricaemia may occur as a consequence of the extensive purine catabolism which accompanies medicine induced rapid cell kill of highly chemosensitive neoplasms (tumour lysis syndrome). Hydration, urine alkalinisation and allopurinol administration will help to prevent or minimise the adverse effects of hyperuricaemia.

Intravesicular 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. These ADRs are mostly reversible.

Infections and infestations. Pneumonia.

Respiratory, thoracic and mediastinal disorders. Pulmonary embolism.

Severe or life-threatening reactions.

Myelosuppression.

This accompanies effective epirubicin hydrochloride treatment in almost 100% of patients and represents the acute dose limiting toxicity of this drug. Leucopenia is the predominant effect with thrombocytopenia and anaemia occurring less frequently. Leucopenia is usually more severe after administration of high dose regimens. Under these conditions, appropriate bone marrow support (e.g. peripheral blood progenitor cells and/or colony stimulating factors) may be required. Intravenous antibiotics should be given in the presence of febrile neutropenia.

Myelosuppression is more common in patients who have had extensive radiotherapy, bone marrow infiltration by tumour or impaired liver function (when appropriate dosage reduction has not been adopted) (see Section 4.2 Dose and method of administration).

Other haematological.

The occurrence of secondary acute myelogenous leukaemia, with or without a preleukaemic phase, has been reported in patients treated with topoisomerase II inhibitors, including anthracyclines such as epirubicin. Secondary leukaemia is more common when such drugs are given in combination with DNA damaging antineoplastic agents, or when patients have been heavily pretreated with cytotoxic drugs. This complication has been reported in 1 to 2% of patients receiving epirubicin containing combination chemotherapy as adjuvant therapy in breast cancer. These leukaemias can have a short (one to three year) latency period.

Mucositis.

This is frequent and painful and most commonly develops five to ten days after treatment. It typically begins as a burning sensation in the mouth and pharynx. The mucositis may involve the vagina, rectum and oesophagus, and progress to ulceration with a risk of secondary infection. Nausea and vomiting may be prevented or alleviated by the administration of appropriate antiemetic therapy. The mucositis usually subsides in ten days.

Cardiotoxicity.

The cardiac abnormalities caused by treatment can be separated into two categories: (i) ECG alterations, and (ii) congestive heart failure (CHF).

ECG changes following epirubicin hydrochloride treatment occur in about 10% of patients. The changes are usually reversible and do not appear to be related to the subsequent development of congestive cardiac failure.

Epirubicin, like other members of this class of drugs, may cause congestive cardiac failure (cardiomyopathy). This effect is cumulative dose dependent and represents the cumulative dose limiting toxicity of the drug. The following measures may identify patients with early

anthracycline cardiomyopathy: progressive flattening or inversion of the T waves (mainly in the left precordial leads), low QRS voltage, prolonged systolic time interval, reduced ejection fraction (echocardiography or by cardiac gated pool scanning) or cardiac biopsy showing characteristic electromicroscopic changes. Early diagnosis and management may control the heart failure. Epirubicin hydrochloride induced cardiomyopathy can be fatal (see Section 4.4 Special warnings and precautions for use). Delayed cardiac toxicity is represented by a characteristic cardiomyopathy, which clinically is manifested by symptoms/ signs of ventricular dysfunction/CHF (such as dyspnoea, pulmonary oedema, dependent oedema, hepatomegaly, ascites, pleural effusion, gallop rhythm).

Delayed cardiotoxicity mainly develops during the course of therapy with epirubicin hydrochloride and up to two to three months afterwards, but late events (several months to years after treatment termination) have occurred. Pericardial effusion has also been described.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9. OVERDOSE

A 36 year old man with non-Hodgkin's lymphoma received daily epirubicin injection 95 mg/m^2 for five consecutive days. Five days later, he developed bone marrow aplasia, grade 4 mucositis and gastrointestinal bleeding. No signs of acute cardiac toxicity were observed. He was treated with antibiotics, colony stimulating factors and antifungal agents and recovered completely. A 63 year old woman with breast cancer and liver metastasis received a single dose of epirubicin 320 mg/m^2, which resulted in hyperthermia, multiple organ failure (respiratory and renal), lactic acidosis, increase lactate dehydrogenase and anuria, and death within 24 hours of administration.

Additional instances of administration of doses higher than recommended have been reported at doses ranging from 150 to 250 mg/m^2. The observed adverse events in these patients were qualitatively similar to known toxicities of epirubicin. Most of the patients recovered with appropriate supportive care.

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

If an overdose occurs, supportive treatment (including antibiotic therapy, blood and platelet transfusions, colony stimulating factors and intensive care as needed) should be provided until the recovery from toxicities. Delayed cardiac failure may occur up to six months after the overdose. Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines.

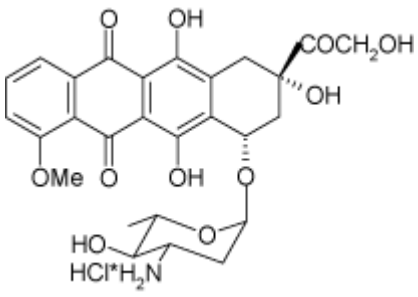
Epirubicin cannot be removed by dialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Structurally, epirubicin hydrochloride differs from doxorubicin hydrochloride only in the orientation of the hydroxyl group at the 4 position on the aminoglycoside ring.



Molecular formula: $C_{27}H_{29}NO_{11}.HCl$

Molecular weight: 579.99

CAS: 56390-09-1

Mechanism of action

The mechanism of action of epirubicin hydrochloride has not been fully elucidated but is probably related to its ability to bind DNA. Cell culture studies have shown cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin hydrochloride has proved to be active on the following experimental tumours: L 1210 ascites and P388 leukaemias, sarcoma SA 180 (solid and ascitic forms), melanoma B 16, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38.

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

Like most other anti-tumour and immunosuppressant agents, epirubicin hydrochloride, under experimental conditions, has mutagenic properties and is carcinogenic in laboratory animals. (see Section 4.6 Fertility, pregnancy and lactation – Use in pregnancy).

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

Clinical trials

Early breast cancer. Data from two multicentre, randomised phase III studies support the use of epirubicin hydrochloride 100 to 120 mg/m^2 for the adjuvant treatment of patients with axillary node positive breast cancer and no evidence of distant metastatic disease (stage II or III). In one study, an intensive cyclophosphamide/ epirubicin/ fluorouracil (CEF-120) regimen (epirubicin given in a dose of 60 mg/m^2 on days 1 and 8) was compared with a conventional cyclophosphamide/ methotrexate/ fluorouracil (CMF) regimen. A total of 716 patients were

randomised, 356 to CEF and 360 to CMF. Both disease free survival and overall survival were significantly prolonged in the CEF arm at five years. Disease free survival was 62% for CEF versus 53% for CMF ($p = 0.01$) and overall survival was 77% for CEF versus 70% for CMF ($p = 0.043$).

In the second study, 301 patients were randomised to receive tamoxifen 20 mg/day alone for four years and 303 patients were randomised to receive tamoxifen for four years in combination with epirubicin 50 mg/m^2 on days 1 and 8 every four weeks for six cycles. Although there was no significant difference between the two arms with regard to disease free survival and overall survival, there was a trend in favour of the combined use of epirubicin and tamoxifen. Disease free survival at two years was 85.1% versus 77.9% and at five years 70.4% versus 59% ($p = 0.07$). Overall survival at 2 years was 93% versus 92% and at 5 years was 78.8% versus 72.9%.

Advanced breast cancer. Data from four open label, multicentre, phase III studies support the use of epirubicin hydrochloride for the treatment of patients with locally advanced or metastatic breast cancer. In Study 1, an intensified cyclophosphamide/ epirubicin/ fluorouracil (CEF-100) regimen (epirubicin given in a dose of 50 mg/m^2 on days 1 and 8) was compared with a conventional CMF regimen ($n = 461$). Studies 2 and 3 compared cyclophosphamide/ epirubicin/ fluorouracil regimens where only the dose of epirubicin varied. In both of these, epirubicin was given in a dose of 50 mg/m^2 on day 1 and compared with either 100 mg/m^2 on day 1 ($n = 456$) or 50 mg/m^2 on days 1 and 8 ($n = 164$). High dose epirubicin (135 mg/m^2) was compared to conventional dose epirubicin (75 mg/m^2) in study 4 ($n = 151$).

The efficacy endpoints included response rate (RR), duration of response (DR), time to tumour progression (TTP), time to treatment failure (TTF), and overall survival (OS). In study 1, the CEF-100 regimen produced a significantly higher RR, a significantly longer TTP and a significantly longer TTF than the CMF regimen. In studies 2, 3 and 4, the higher dose epirubicin containing regimens produced a significantly greater RR than the lower dose epirubicin containing regimens. DR and TTF were also significantly longer in study 3 and TPP was significantly longer in study 4 for the higher dose epirubicin regimens.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

When epirubicin hydrochloride is administered intravesically, the systemic absorption is minimal.

There is evidence for a dose response and dose toxicity relationship for epirubicin in breast cancer, and to a lesser extent for lymphoma. This relationship is steeper and therefore more evident for doses of epirubicin above 90 mg/m^2. Current data indicates that an increase in dose (for dose intensity) produces greater response rates.

Epirubicin hydrochloride is immunosuppressive in animals. Although there are no clinical data on the immunosuppressive effects of epirubicin, effects similar to those seen with doxorubicin may be expected.

Distribution

As with doxorubicin, epirubicin hydrochloride may not be expected to cross the blood brain barrier.

Metabolism

No data available.

Excretion

In patients with normal hepatic and renal function, plasma levels after intravenous injection of 75 to 90 mg/m^2 of the drug follow a triexponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. Plasma levels of the drug's main metabolite, the 13-OH derivative, are constantly somewhat lower and virtually parallel to those of the unchanged drug. Epirubicin hydrochloride is eliminated mainly through the liver; high plasma clearance values (0.9 L/minute) indicate that the slow elimination of epirubicin is due to extensive tissue distribution. Urinary excretion accounts for approximately 11% of the administered dose in 48 hours. However, like doxorubicin, biliary excretion is likely to be the major excretion route. Impairment of liver function delays plasma clearance.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

Secondary acute myelogenous leukaemia (AML) has been reported in patients treated with anthracyclines; risk of refractory AML increases when epirubicin is combined with other DNA damaging antineoplastics, when patients have had extensive exposure to cytotoxic drugs, or when anthracycline doses have been escalated. The cumulative risk for adjuvant Epirubicin therapy related leukemia is estimated as 0.2 and 0.8% at three and five years, respectively.

Epirubicin was mutagenic *in vitro* to bacteria (Ames test) either in the presence or absence of metabolic activation and to mammalian cells (HGPRT assay in V79 Chinese hamster lung fibroblasts) in the absence but not in the presence of metabolic activation. Epirubicin was clastogenic *in vitro* (chromosome aberration in human lymphocytes) both in the presence and absence of metabolic activation and was also clastogenic *in vivo* (chromosome aberration in mouse bone marrow).

Carcinogenicity

Epirubicin is carcinogenic in animals. Conventional long-term animal studies to evaluate the carcinogenic potential of epirubicin have not been conducted, but intravenous administration of a single 3.6 mg/kg epirubicin dose (0.16-times the maximum recommended clinical dose based on body surface area) to female rats approximately doubled the incidence of mammary tumours (primarily fibroadenomas) observed at 1 year. Administration of 0.5 mg/kg epirubicin intravenously (0.02-times the maximum recommended clinical dose based on body surface area) to rats every 3 weeks for ten doses increased the incidence of subcutaneous fibromas in males over an 18-month observation period. In addition, subcutaneous administration of 0.75 or 1.0 mg/kg/day to newborn rats for 4 days on both the first and tenth day after birth for a total of eight doses increased the incidence of animals with tumours compared to controls during a 24-month observation period.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Sodium chloride, water for injections, and dilute hydrochloric acid (as necessary to adjust pH)

6.2. INCOMPATIBILITIES

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

It is not recommended that it be mixed with these drugs in the same container.

Epirubicin hydrochloride should not be mixed with heparin, as these drugs are incompatible. Until specific compatibility data are available, it is not recommended that epirubicin hydrochloride be mixed with other drugs.

6.3. SHELF LIFE

24 months from date of manufacture.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store at 2 °C to 8 °C (Refrigerate. Do not freeze). Protect from light.

Storage of the medicinal product 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). Solution for injection should be used within 24 hours after removal from refrigeration.

6.5. NATURE AND CONTENTS OF CONTAINER

Solution for injection (clear red solution, vials),

10 mg in 5 mL glass vials: 1’s

50 mg in 25 mL glass vials: 1's

100 mg in 50 mL glass vials: 1’s

200 mg in 100 mL glass vials: 1's

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Pharmaceutical precautions

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

Personnel should be trained in good technique for handling.

Pregnant staff should be excluded from working with this drug.

Personnel handling epirubicin hydrochloride should wear protective clothing: goggles, gowns and disposable gloves and masks.

A designated area should be defined for reconstitution (preferably under a laminar flow containment system). The work surface should be protected by disposable plastic backed absorbent paper.

All items used for administration or cleaning, including gloves should be placed in high risk, waste disposal bags for high temperature incineration.

Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water.

All cleaning materials should be disposed of as indicated previously.

Accidental contact with the eyes or skin should be treated immediately. Copious lavage with water is appropriate treatment for contact with the eyes, whereas water or soap and water, or sodium bicarbonate solution may be used on the skin; medical attention should be sought.

Epirubicin is for use in one patient on one occasion only. Discard any residue.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand

Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

01/05/2015

10. DATE OF REVISION OF THE TEXT

11/06/2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Minor editorial changes Addition of information regarding embryo-fetal toxicity
4.6	Addition of information regarding reproductive toxicity, pregnancy, lactation and recommendation for fertility preservation
4.8	Minor editorial change Updated AE reporting URL to https://pophealth.my.site.com/carmreportnz/s/
5.3	Updated information regarding genotoxicity and carcinogenicity