Summary of Product Characteristics

1. Name of the medicinal product

Drug Product	**:**	Epirubicin Injection BP (50 mg/ 25 mL)
Generic Name	**:**	Epirubicin Injection BP
Strength	**:**	Each mL of sterile preservative free Isotonic aqueous solution containing 2.0 mg of Epirubicin Hydrochloride BP in 1.0 mL of Water for Injection USP

2. Quality and Quantitative Composition

Each mL contains:

Epirubicin Hydrochloride BP	2.0 mg
Water for Injection USP	qs.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Sterile preservative free Isotonic aqueous solution for Intravenous use

4. Clinical Particulars

4.1 Therapeutic Indications

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

• Breast, ovarian, gastric, lung and colorectal carcinomas

• Malignant lymphomas

• Leukaemias

• Multiple myeloma.

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 is for intravenous or intravesical use only. Epirubicin is not active when given orally and should not be injected intramuscularly or intrathecally.

Intravenous administration

It is advisable to administer epirubicin hydrochloride 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.

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 haematomedullary status.

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

Lung cancer

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

• Small cell lung cancer (previously untreated): 120 mg/m2 day 1, every 3 weeks.

• Non-small cell lung cancer (squamous, large cell, and adenocarcinoma previously untreated): 135 mg/m2 day 1 or 45 mg/m2 day 1, 2 and 3 every 3 weeks.

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.

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.

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.

Bone marrow impairment

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.

Combination therapy

If epirubicin hydrochloride is used in combination with other cytotoxic products, the dose should be reduced accordingly.

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 µmol/l	50%
> 51 µmol/l	75%

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.

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. Epirubicin hydrochloride has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours to prevent recurrence.

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 (chemical cystitis) is observed: A dose reduction to 30 mg/50 ml is advised.

Carcinoma-in-situ: 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.

DILUTION TABLE FOR BLADDER INSTILLATION SOLUTIONS

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

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 urine at the end of the instillation time.

4.3 Contraindications

Epirubicin is contraindicated in:

• Patients who have demonstrated hypersensitivity to epirubicin or to any of the excipients, and/or other anthracyclines or anthracenediones

• Lactation

For Intravenous use, epirubicin is contraindicated in:

• Patients with persistent myelosuppression or myelosuppression induced by previous treatment with either other anti-neoplastic agents or radiotherapy

• Patients with severe hepatic impairment

• Patients previously treated with maximum cumulative doses of epirubicin and/or other anthracyclines (doxorubicin or daunorubicin) and anthracenediones

• Patients with current or previous history of cardiac impairment such as those who exhibit severe arrhythmias, severe myocardial insufficiency, recent myocardial infarction, myocardiopathy and patients with unstable angina pectoris

• Patients with acute systemic infections

For Intravesical use, epirubicin is contraindicated in:

• Patients with urinary tract infections

• Patients with inflammation of the bladder

• Patients who have invasive tumours penetrating the bladder

• Patients with catheterisation problems

• Patients with haematuria

4.4 Special warning and precautions for use.

Epirubicin should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of epirubicin.

Careful baseline monitoring of various laboratory parameters and cardiac function should precede initial treatment with epirubicin.

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

While treatment with high doses of epirubicin 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 requires 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. The effects are rarely considered for clinical significance and are generally not taken as indications to discontinue treatment with epirubicin.

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 induced by anthracyclines is associated with persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the left ventricular ejection fraction (LVEF). Other signs and symptoms that have been reported include congestive heart failure (CHF) such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion and gallop rhythm. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.
The risk of developing CHF is increased in those patients who receive higher cumulative doses of epirubicin hydrochloride in excess of 900 mg/m2. Given the risk of cardiomyopathy, this cumulative dose should only be exceeded with extreme caution.

Heart failure may appear several weeks after discontinuing epirubicin therapy and may be unresponsive to specific medical treatment.

Cardiac function should be assessed in patients prior to undergoing treatment with epirubicin and must be continuously monitored during the course of treatment to minimise the risk of incurring severe cardiac impairment. The risk may be reduced with the prompt termination of epirubicin at the first sign of impaired function by regularly monitoring the LVEF during the course of treatment.

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 a MUGA scan or either an ECHO is recommended, particularly in those patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed particularly for those patients who receive higher cumulative anthracycline doses. The technique used in the evaluation for cardiac function should be consistent throughout the follow-up.

The potential risk of cardiotoxicity may increase in those patients who exhibit active or dormant cardiovascular disease, and in those who received previous or concomitant radiotherapy to the mediastinal/ pericardial areas. This includes previous therapy with other anthracyclines or anthracenediones, and the concomitant use of other drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab). 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 an 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.

Cardiac function monitoring must be assessed in patients receiving higher cumulative doses and in those with risk factors. However, cardiotoxicity may occur following lower cumulative doses of epirubicin whether or not cardiac risk factors have been identified. It is probable that the toxicity of epirubicin and other anthracyclines or anthracenediones is additive.

Haematologic Toxicity - As with other cytotoxic agents, epirubicin may produce myelosuppression. Haematologic profiles should be assessed both before and during each cycle of therapy with epirubicin, including differential white blood cell (WBC) counts, red blood cell, neutrophil and platelet counts. A

dose-dependent, reversible leucopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopenia and neutropenia are generally more severe with high-dose schedules, reaching a nadir in most cases between days 10 and 14 following drug administration. However, this is usually transient with the WBC/neutrophil counts returning to normal values in most cases by day 21. Thrombocytopenia (<100,000 platelets/mm3) is reported in very few patients and anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicemia, septic shock, haemorrhage, 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 or in combination with radiation treatment, or patients have been heavily pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. This type of leukemia can have a 1 to 3-year latency period.

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

Liver Function - The major route of elimination of epirubicin is the hepatobiliary system. Therefore serum total bilirubin and alkaline phosphatise levels (AST and ALT) should be evaluated prior to initiating treatment and during the course of treatment. Patients with elevated bilirubin or AST levels may experience slower clearance of epirubicin, which may lead to an increased toxicity. For those patients a lower dose is recommended . Patients with severe hepatic impairment should not be treated with epirubicin .

Renal Function - For patients with reduced renal function serum creatinine levels should be assessed prior to and during therapy. For those patients with increased serum creatinine levels (> 5 mg/dL) a dosage reduction is necessary.

Epirubicin may impart a red colour to the urine for one or two days following administration.

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.

Extravasation - Extravasation of epirubicin from the vein during intravenous administration may cause local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Should signs or symptoms of extravasation occur during intravenous administration of epirubicin, the drug infusion should be immediately discontinued. The patient's pain may be relieved by cooling down the area and keeping it cool for 24 hours. The patient should be monitored closely during the subsequent period of time, as necrosis may occur several weeks after 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.

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

Reproductive system - Epirubicin can cause genotoxicity. Men and women treated with epirubicin should adopt appropriate contraceptive methods. 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, haematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterisation problems (e.g., uretheral obstruction due to massive intravesical tumours).

Intra-arterial route - Intra-arterial administration of epirubicin (transcatheter arterial embolisation for the localised or regional therapies of primary hepatocellular carcinoma or liver metastases) may produce (in addition to systemic toxicity qualitatively similar to that observed following intravenous administration of epirubicin) localised or regional events which include gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to drug-induced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue and is not recommended.

4.5 Interaction with other medicinal products and other form of interactions

It is not recommended that Epirubicin Hydrochloride 2 mg/ml Injection be mixed with other medicinal products.

Epirubicin can be used in combination with other anti-cancer agents but patients should be monitored for additive toxicity. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastro-intestinal effects. 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 metabolised by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

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 discontinuing treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at high 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 discontinuing trastuzumab. If

anthracyclines are used before this length of time, careful monitoring of cardiac function is recommended.

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.

Drug interactions with epirubicin have been observed with cimetidine, dexverapamil, dexrazoxane, docetaxel, interferon alfa-2b, paclitaxel and quinine.

Cimetidine 400 mg b.i.d given prior to epirubicin 100 mg/m2 every 3 weeks led to a 50% increase in epirubicin AUC and a 41% increase in epirubicinol AUC (latter $p<0.05$). The AUC of the 7-deoxy-doxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P-450 activity. Cimetidine 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.

Co-administration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when epirubicin was administered prior to the taxane. In one study, haematological toxicity was greater when paclitaxel was administered before epirubicin compared with after epirubicin.

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 following 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 alfa-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 and antiretroviral agents).

4.6 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 necessary, seek medical advice on sperm preservation due to the possibility of irreversible infertility caused by the therapy.

Due to the genotoxicity effects of epirubicin, male patients are advised not to father a child during and up to 6-months following the discontinuation of epirubicin treatment.

Epirubicin may cause amenorrhoea or premature menopause in premenopausal women.

Pregnancy

Both men and women receiving epirubicin should be informed of the potential risk of adverse effects on reproduction. Experimental data in animals suggest that epirubicin may cause foetal harm when administered to a pregnant woman.

There are no studies in pregnant women. Women of childbearing potential should be fully informed of the potential risks to the foetus should they become pregnant during epirubicin therapy. In cancer chemotherapy, epirubicin should not be used in pregnant women or women of childbearing potential who might become pregnant unless the potential benefits to the mother outweigh the possible risks to the foetus.

Lactation

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.
Epirubicin should not normally be administered to patients who are breast-feeding.

4.7 Effects on ability to drive and use machine

There have been no reports of particular adverse events relating to the effects on ability to drive and to use machines. The effect of epirubicin on the ability to drive or use machinery has not been systematically evaluated.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with epirubicin 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 (cannot be estimated form 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 and 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 leukemia, acute myelogenous leukemia
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 myelosoppression.
Immune system disorders	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common	Anorexia, dehydration
	Rare	Hyperuricemia
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, arrythmias, cardiomyopathy), ventricular tachycardia, bradycardia, AV block, bundle-branch block
Vascular disorders	Common	Hot flushes
	Uncommon	Phlebitis, thrombophebitis
	Not known	Shock, thromboembolism, including pulmonary emboli
Gastrointestinal disorders	Common	Mucositis, oesophagitis, stomatitis, vomiting, diarrhoea, nausea
Skin and subcutaneous tissue disorders	Very Common	Alopecia (accompanied by lack of beard growth in males)
	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	Amenorrhoea, azoospermia
General disorders and administration site conditions	Common	Infusion site erythema
	Rare	Malaise, asthenia, fever, chills
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

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. These ADRs are mostly reversible.

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 EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdosage

Acute overdosage with epirubicin will result in severe myelosuppression within 10-14 days (mainly leucopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and cardiac complications (acute myocardial degeneration within 24 hours). Treatment should aim to support the patient during this period and should utilise such measures as blood transfusion and reverse barrier nursing. Latent cardiac failure has been observed with anthracyclines several months (up to 6 months) to years after completion of treatment. Patients should 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 Pharmacodynamics Properties

Pharmacotherapeutic group: Antineoplastic agent. ATC code: L01D B03

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 Pharmacokinetics 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. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.

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 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 injection

6.2 Incompatibilities

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug, which includes sodium bicarbonate containing solutions. Neither the injection nor any diluted solution should be mixed with any other drugs. (A physical incompatibility with heparin has been reported).

Epirubicin should not be mixed with other drugs.

6.3 Shelf life

24 months from date of manufacturing

In use: Epirubicin Hydrochloride 2 mg/ml Injection may be further diluted, under aseptic conditions, in Glucose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. After dilution, physical and chemical in-use stability has been demonstrated for:

Diluent	Target Concentration	Storage Conditions	Time period
0.9% sodium chloride solution for infusion	0.2 mg/ml and 1.0 mg/ml	2-8°C in the absence of light in PVC infusion bags	84 days
5% glucose solution for infusion	0.2 mg/ml and 1.0 mg/ml	2-8°C in the absence of light in PVC infusion bags	84 days
0.9% sodium chloride solution for infusion	0.2 mg/ml and 1.0 mg/ml	25°C under normal lighting conditions in PVC infusion bags	14 days
5% glucose solution for infusion	0.2 mg/ml and 1.0 mg/ml	25°C under normal lighting conditions in PVC infusion bags	14 days

From a microbiological point of view however, 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 protected from light at a temperature between 2º to 8º (36°F to 45º F).

6.5 Special precautions for disposal and other handlings

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.

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.

6.5. Nature and contents of container

Container Closure System for Epirubicin Injection BP (50 mg / 25 mL)

30 mL Amber Glass Vial USP Type I

20 mm Bromo butyl rubber plug

20 mm Golden Lacquered Aluminium flip off seal

7. Marketing authorisation holder

Beta Drugs Limited
Kharuni-Lodhimajra Road,
Vill: Nandpur, Baddi, Distt. Solan,
Himachal Pradesh, 173205 INDIA

8. Marketing authorisation number(s)

07488/08155/NMR/2020

9. Date of first authorisation

02 Jun 2022

10. Date of revision of the text

July 2024