

# PACKAGE INSERT TEMPLATE FOR EPIRUBICIN HYDROCHLORIDE INTRAVESICAL INJECTION & INTRAVENOUS INFUSION

## Brand or Product Name

[Product name] ...mg/ml Injection

[Product name] ...mg/ml Vials

## Name and Strength of Active Substance(s)

Epirubicin hydrochloride ....mg/ml

[Example of strengths: 10mg/5ml , 50mg/25ml, 200mg/100ml, 20mg/10ml]

## Product Description

[Visual description of the appearance of the product (eg colour etc)

eg Clear red solution

## Pharmacodynamics

Epirubicin is an anthracycline derivative of doxorubicin that exerts its cytotoxic effects by intercalating DNA (inhibits nucleic acid and protein synthesis) and inhibiting DNA helicase activity (prevents replication and transcription. Generation of cytotoxic free radicals is another possible mechanism of action for epirubicin.

## Pharmacokinetics

### *Distribution*

Protein binding: 77%

Epirubicin is rapidly and widely distributed into body tissues following intravenous administration

Epirubicin does not cross the blood-brain barrier.

### *Metabolism*

Undergoes extensive metabolism in the liver, with the formation of epirubicinol (13-hydroxyepirubicin) and appreciable amounts of glucuronide derivatives.

### *Excretion*

Renal excretion: 20% to 27%

About 6% is eliminated via the kidney as unchanged drug with the remainder as epirubicinol and other metabolites

Epirubicin is eliminated mainly in bile, with a terminal plasma elimination half-life of about 30 to 40 hours

Total body clearance: 1 to 1.5 l/minute

## Indication

Epirubicin 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;
- superficial bladder cancer (Tis; Ta)

In bladder cancer, Epirubicin 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).

### **Recommended Dosage**

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

Care in the intravenous administration of Epirubicin will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions, such as urticaria and erythematous streaking.

NOTE: The recommended lifetime cumulative dose limit is 1000 mg Epirubicin/m<sup>2</sup> body surface area.

### ***Intravenous Administration***

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<sup>2</sup>. 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 physician should determine the choice of dose.

Higher doses, up to 135 mg/m<sup>2</sup> as a single agent and 120 mg/m<sup>2</sup> in combination, every 3-4 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<sup>2</sup> to 120 mg/m<sup>2</sup> every 3-4 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 75-90 mg/m<sup>2</sup>) for heavily pre-treated patients, patients with pre-existing bone marrow depression or in the presence of neoplastic bone marrow infiltration. If Epirubicin is used in combination with other cytotoxic drugs with potentially overlapping toxicities, the recommended dose per cycle should be reduced accordingly.

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).

### ***Intravesical Administration***

For the treatment of papillary transitional cell carcinoma of the bladder, a therapy of 8 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, 4 weekly administrations of 50 mg followed by 11 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 twelve 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.

### ***Dose Modifications***

As clinical toxicity may be increased by the presence of impaired liver function, Epirubicin dosage must be reduced if hepatic function is impaired, according to the following table:

### Serum Bilirubin Levels

20 - 50 µmol/L

Over 50 µmol/L

### Recommended Dose

1/2 normal dose

1/4 normal dose

Haematological toxicity may require dose reduction, delay or suspension of Epirubicin therapy. Lower doses may be necessary if Epirubicin is used concurrently with other anti-neoplastic agents.

## **Mode of Administration**

### ***Intravenous Administration***

It is recommended that Epirubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection or 5% Glucose Injection. 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 administered in not less than 3 to 4 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.

### ***Intravesical Administration***

Epirubicin, to be instilled using a catheter, should be retained intravesically for 1 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.

## **Contraindications**

*Situations in which patients should not be treated with intravenous Epirubicin are:*

- hypersensitivity to epirubicin, other anthracyclines or anthracenediones;
- 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 myocardial insufficiency, previous myocardial infarction);
- previous treatments with maximum cumulative doses of mitozantrone, mitomycin C or other anthracyclines, such as doxorubicin or daunorubicin;
- pregnancy and lactation.

*Contraindications for intravesical use are:*

- invasive tumours that have penetrated the bladder wall;
- urinary infections;
- inflammation of the bladder;
- catheterisation problems;
- haematuria.

## **Warnings and Precautions**

*[Specific package insert requirement for epirubicin]*

**CAUTION : CYTOTOXIC AGENT**

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

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

Care in the intravenous administration of Epirubicin will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions, such as urticaria and erythematous streaking.

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 (e.g.  $\geq 90$  mg/m<sup>2</sup> every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (e.g.  $< 90$  mg/m<sup>2</sup> every 3 to 4 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 requires close observation of the patient and extensive laboratory monitoring including assessment of cardiac function. 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 treatment. The routine assessment of cardiac function may include electrocardiogram (ECG) and the evaluation of left ventricular ejection fraction (LVEF).

Epirubicin 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 3 to 4 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 injection into a small vessel or from repeated injections into the same vein.

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

Epirubicin is not an antimicrobial agent.

#### *Haematological Considerations*

Haematological monitoring should be undertaken regularly in view of the possibility of severe bone marrow depression which may occur. Leukopenia is usually transient with the recommended dosage schedules, reaching a nadir between 10 and 14 days after administration. A return to normal blood values usually occurs within 21 days from administration.

Secondary acute myelogenous leukaemia, with or without a pre-leukaemic phase, has been reported in patients treated with topoisomerase II inhibitors, including anthracyclines such as epirubicin.

#### *Anthracycline Induced Cardiotoxicity*

Patients receiving Epirubicin should be monitored for anthracycline-induced cardiotoxicity.

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. 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. 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 hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Life-threatening

CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

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

The onset of cardiac failure may be sudden and early recognition may increase the likelihood of benefit from treatment. Heart failure has been reported even several weeks to several months after discontinuing treatment and the risk may be higher in patients with active or dormant cardiovascular disease, concomitant or previous radiation of the mediastinal-pericardial area, hypertensive cardiomyopathy, previous therapy with other anthracyclines or anthracenediones or cardiotoxic agents (e.g. trastuzumab, high dose cyclophosphamide or 5-fluorouracil). 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 and may persist in the circulation for up to 24 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 24 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

In such patients a reduction of the total cumulative dose may be required and the monitoring of cardiac function must be particularly strict. The risk-benefit of continuing Epirubicin treatment under conditions of impaired cardiac function has to be carefully evaluated. However, cardiotoxicity with Epirubicin may occur at lower cumulative doses whether or not cardiac risk factors are present. It is probable that the toxicity of Epirubicin and other anthracyclines or anthracenediones is additive.

The total (cumulative) dose levels of Epirubicin do correlate with the incidence of drug-induced congestive cardiac failure (cardiomyopathy). At a cellular level the nature of Epirubicin-induced cardiac toxicity appears to be similar to that of doxorubicin. Limitation of the total dose of Epirubicin to 900 mg/m<sup>2</sup> in good risk patients reduces the likelihood of drug-induced cardiomyopathy. It is suggested that an ECG be taken before treatment. Alterations of the ECG, such as flattening or inversion of the T wave, depression of the S-T segment or the onset of arrhythmias, are generally transient and reversible and need not necessarily indicate that treatment should be stopped. It is also advisable to assess cardiac function by other techniques, such as echocardiography and measurement of the ejection fraction by radionuclide angiography. The technique should be consistent throughout follow-up.

#### *Hepatotoxicity*

As toxicity of Epirubicin 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. Serum total bilirubin and AST levels should be evaluated before and during treatment with Epirubicin. Patients with severe hepatic impairment should not receive Epirubicin.

#### *Renal toxicity*

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Epirubicin 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 .

#### *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.

### *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.

Epirubicin 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.

Like other cytotoxic drugs, Epirubicin may induce hyperuricaemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

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

### *Effects on ability to drive and use machines*

There have been no reports of particular adverse events relating to the effects on ability to drive and to use machines. However, epirubicin may cause episodes of nausea and vomiting, which can temporarily lead to an impairment of ability to drive or operate machines.

### **Interactions with Other Medicaments**

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

In addition, the concomitant use of Epirubicin 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), requires a close monitoring of cardiac function throughout treatment.

### *Cimetidine*

Interaction Effect: an increased risk of epirubicin toxicity (myelosuppression, cardiotoxicity). Cimetidine increased the AUC of Epirubicin by 50% and should be stopped during treatment with Epirubicin.

When given prior to epirubicin, paclitaxel can cause increased plasma concentrations of unchanged epirubicin. Coadministration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when epirubicin was administered prior to the taxane.

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

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

Cardiotoxic drugs: Concurrent administration of epirubicin hydrochloride and cardiotoxic drugs such as propranolol and calcium channel blockers may precipitate CHF.

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

Verapamil: increased risk of heart failure

Live Vaccines: The use of live attenuated vaccines in the presence of immunosuppression may increase the risk and severity of infection in response to the vaccine. Such vaccinations should only be administered with due regard for these theoretical risks.

### **Statement on Usage During Pregnancy and Lactation**

#### *Pregnancy*

There are no adequate and well-controlled studies in pregnant women. Based on toxicities evident in animal studies, epirubicin can cause fetal harm when administered to a pregnant woman. Advise women of childbearing potential to avoid becoming pregnant while receiving epirubicin therapy. If this drug is used during pregnancy or if the patient becomes pregnant while receiving the drug, inform the patient of the potential fetal risks

#### *Lactation*

It is not known whether epirubicin is excreted into human breast milk and the potential for adverse effects in the nursing infant from exposure to the drug are unknown. Because other anthracyclines have been found in human breast milk, breastfeeding should be discontinued prior to initiation of therapy with epirubicin.

#### ***Carcinogenicity, Mutagenicity, Impairment of Fertility***

Although no studies have been conducted with epirubicin hydrochloride, it may be expected, like doxorubicin, to cause infertility during the period of drug administration. 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 azospermia 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 employ contraceptive measures.

Epirubicin is mutagenic, clastogenic, and carcinogenic in animals

#### **Adverse Effects / Undesirable Effects**

Cardiovascular effects: anthracycline-induced cardiac toxicity is manifested by early or delayed events. Early toxicity of epirubicin consists mainly of cardiac arrhythmias and electrocardiogram (ecg) changes. Arrhythmias also include premature ventricular contractions, sinus tachycardia, bradycardia, bundle-branch block, and atrioventricular junctional premature beats. Cardiomyopathy, Congestive heart failure, (tachycardia; pulmonary edema; dyspnea; lower extremity edema; ascites; gallop rhythm; hepatomegaly; pleural effusion) , thrombophlebitis.

Dermatologic effects: alopecia, hyperpigmentation of skin and nails, injection site extravasation, itching, photosensitivity, hypersensitivity of irradiated skin (radiation-recall reaction), rash, urticaria , flushes.

Gastrointestinal effects: diarrhea, inflammatory disease of mucous membrane ( mucositis, mainly stomatitis),loss of appetite, nausea and vomiting, Oesophagitis. Hyperpigmentation of the oral mucosa, abdominal pain or burning sensation.

Hematologic effects: myelosuppression, particularly leukopenia and neutropenia, anemia, thrombocytopenia, and rarely secondary acute myelogenous leukemia.

Immunologic effects: anaphylaxis, immune hypersensitivity reaction (signs and symptoms of hypersensitivity reactions range from skin rash and pruritus to fever, chills, and shock).

Neurologic effects: central nervous system finding (headache, dizziness, and lethargy peripheral neuropathy).

Renal effects: nephrotoxicity (proteinuria).

Hepatic effects: changes in transaminase levels

Reproductive system and breast disorders: Amenorrhoea, azoospermia.

General: hyperuricaemia (as a result of rapid lysis of neoplastic cells). hyperpyrexia, malaise, and weakness.

### **Overdose and Treatment**

Very high single doses of Epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 days and also 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 of toxicities. Delayed cardiac failure may occur up to 6 months after the overdose. Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines.

### **Incompatibilities**

*[To add appropriate information based on formulation]*

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

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

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

### **Instructions for Use**

*[To add appropriate information and graphic]*

### **Storage Conditions**

*[ eg Store below.... °C ]*

### **Dosage Forms and Packaging Available**

*[ Packaging type & pack size]*

### **Name and Address of Manufacturer**

*[ Name & full address of manufacturer ]*

### **Name and Address of Marketing Authorization Holder**

*[ Name & full address of marketing authorization holder ]*

### **Date of Revision of Package Insert**

*[ day/month/year ]*