

**Public Assessment Report**

**Decentralised Procedure**

**Epirubicin 2 mg/ml, solution for injection**

**PL 30329/0001**

**UK/H/1033/01/DC**

**Merck Generiques SCS**

## **Lay summary**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Merck Generiques SCS a Marketing Authorisation (licence) for the medicinal product Epirubicin 2 mg/ml, solution for injection (PL 30329/0001).

Epirubicin is an anti-cancer medicine. It is used in the treatment of breast, gastric and bladder cancers. Epirubicin is also used to help prevent recurrence of bladder cancer after surgery.

The data submitted in support of the application for Epirubicin 2 mg/ml, solution for injection raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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## Module 1

### Information about decentralised procedure

Name of the product in the Reference Member State	Epirubicin 2 mg/ml, solution for injection
Name of the active substance (INN)	Epirubicin hydrochloride
Pharmacotherapeutic classification (ATC code)	Antineoplastic agent L01DB03
Pharmaceutical form and strength	2 mg/ml Solution for injection
Reference numbers for the Decentralised Procedure	UK/H/1033/01/DC
Reference Member State	United Kingdom
Member States concerned	AT, BE, DK, EL, FI, NO, PT, SE and SK
Date of start of the procedure	15 May 2007
End date of decentralised procedure	21 May 2008
Marketing Authorisation Number	PL 30329/0001
Name and address of the authorisation holder	Merck Generiques SCS 34 Rue Saint Romain 69359 Lyon Cedex 08 France

## Module 2

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Epirubicin 2 mg/ml, solution for injection

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Epirubicin Hydrochloride 2 mg/ml

1 ml of solution for injection contains 2 mg of epirubicin hydrochloride.

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

Each vial of 10 ml of solution contains 20 mg of epirubicin hydrochloride.

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

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

Epirubicin 2 mg/ml, solution for injection contains sodium (3.6 mg/ml or 0.16 mmol/ml).

For a full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Solution for injection

A clear red solution.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

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

- Breast and gastric carcinomas,

When administered intravesically, epirubicin has been shown to be beneficial in the treatment of:

- Papillary transitional cell carcinoma of the bladder,
- Carcinoma-in-situ,
- Prophylaxis of recurrences after transurethral resection.

##### 4.2 Posology and method of administration

Epirubicin is for intravenous or intravesical use only.

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

###### Intravenous administration

It is advisable to administer epirubicin via the tubing of a free-running intravenous saline or glucose infusion after checking that the needle is properly placed in the vein. Care should be taken to avoid extravasation (see section 4.4). In case of extravasation, administration should be stopped immediately.

###### *Conventional dose*

When epirubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m<sup>2</sup> body area. Epirubicin should be injected intravenously over 3-5 minutes. The dose should be repeated at 21-day intervals, depending upon the patient's haematological status and bone marrow function. If signs of toxicity, including severe neutropenia/neutropenic fever and thrombocytopenia occur (which could persist at day 21), dose modification or postponement of the subsequent dose may be required.

### *Breast Cancer*

In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin ranging from 100 mg/m<sup>2</sup> (as a single dose on day 1) to 120 mg/m<sup>2</sup> (in two divided doses on days 1 and 8) every 3-4 weeks, in combination with intravenous cyclophosphamide and 5-fluorouracil and oral tamoxifen, are recommended.

Lower doses (60-75 mg/m<sup>2</sup> for conventional treatment and 105-120 mg/m<sup>2</sup> 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.

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

<b>Cancer Indication</b>	<b>Epirubicin Dose (mg/m<sup>2</sup>)<sup>a</sup></b>	
	<b>Monotherapy</b>	<b>Combination Therapy</b>
Gastric cancer	60–90	50
Bladder cancer	50 mg/50 ml or 80 mg/50 ml (carcinoma in situ) Prophylaxis: 50 mg/50 ml weekly for 4 weeks then monthly for 11 months	

<sup>a</sup> Doses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals

A total cumulative dose of 900 – 1000 mg/m<sup>2</sup> should not be exceeded due to a potential risk of cardiotoxicity (see section 4.4).

### *Combination therapy*

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

### *Impaired liver function*

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

• Serum Bilirubin	AST*	Dose Reduction
1.4 – 3 mg/100 ml (24 – 51 µmol/l)		50 %
> 3 mg/100 ml (> 51 µmol/l)	> 4 times upper normal limit	75 %

\* AST – aspartate aminotransferase

#### *Impaired renal function*

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted by this route. However, lower starting doses should be considered in patients with severe renal impairment (serum creatinine > 5 mg/dl).

#### Intravesical administration

Epirubicin can be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be given intravesically for the treatment of invasive tumours that have penetrated the bladder wall; systemic therapy or surgery is more appropriate in these situations (see section 4.3). Epirubicin 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 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 required	Volume of 2 mg/ml Epirubicin injection	Volume of diluent (sterile water for injection or 0.9% sterile saline)	Total volume for bladder instillation
30 mg	15 ml	35 ml	50 ml
50 mg	25 ml	25 ml	50 ml
80 mg	40 ml	10 ml	50 ml

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

### 4.3 **Contraindications**

Epirubicin is contraindicated in:

- Patients who have demonstrated hypersensitivity to the active substance or to any of the excipients,
- Patients with marked myelosuppression induced by previous treatment with either other anti-neoplastic agents or radiotherapy,
- Patients treated with maximal cumulative doses of other anthracyclines such as doxorubicin or daunorubicin,
- Patients with current or previous history of cardiac impairment (including 4th degree muscular heart failure, acute heart attack and previous heart attack which led to 3rd and 4th

degree muscular heart failure, acute inflammatory heart diseases, arrhythmia with serious haemodynamic consequences),

- Patients with acute systemic infections,
- Lactation.

Contraindications to the intravesical administration of epirubicin are:

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

#### **4.4 Special warnings 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 management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of epirubicin.

Epirubicin can have genotoxic effects. Therefore, male patients treated with epirubicin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to because of the possibility of infertility due to therapy with epirubicin (see section 4.6).

Women should not become pregnant during treatment with epirubicin. Men and women should use an effective method of contraception during treatment and for six months thereafter (see section 4.6).

Extravasation of epirubicin from the vein during injection may cause severe tissue lesions and necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

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

During treatment with epirubicin, red blood cell, white blood cell, neutrophil and platelet counts should be carefully monitored both before and during each cycle of therapy. Leucopenia and neutropenia are usually transient with conventional and high-dose schedules reaching a nadir between the 10<sup>th</sup> and 14<sup>th</sup> day, values should return to normal by the 21<sup>st</sup> day; they are more severe with high dose schedules. Thrombocytopenia (< 100,000 platelets/mm<sup>3</sup>) is experienced in very few patients, even following high doses of epirubicin.

Patients must have adequately recovered from severe stomatitis or mucositis before starting treatment with epirubicin.

In establishing the maximal cumulative dose of epirubicin, consideration should be given to any concomitant therapy with potentially cardiotoxic drugs. A cumulative dose of 900-1000 mg/m<sup>2</sup>



should only be exceeded with extreme caution with both conventional and high doses of epirubicin. Above this level the risk of irreversible congestive heart failure increases greatly. An ECG is recommended before and after each treatment cycle. Alterations in the ECG tracing, such as flattening or inversion of the T wave, depression of the S-T segment, or the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment. With cumulative doses < 900 mg/m<sup>2</sup>, there is evidence that cardiac toxicity rarely occurs. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart failure of the type described for other anthracyclines. In case of cardiac insufficiency, treatment with epirubicin should be discontinued.

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 ejection fraction. Cardiac monitoring of patients receiving epirubicin treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques.

Electrocardiogram (ECG) changes may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity. The risk of serious cardiac impairment 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 preferred method for repeated assessment of cardiac function is evaluation of LVEF measure by multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increase cardiac toxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through follow-up. In patients with risk factors, particularly prior anthracycline or anthracenedione use, the monitoring of cardiac function must be particularly strict.

Heart failure may appear several weeks after discontinuing therapy with epirubicin and may be unresponsive to specific medical treatment. The potential risk of cardiotoxicity may increase in patients who have received concomitant, or prior, radiotherapy to the mediastinal pericardial area and/or who are under medical treatment with potentially cardiotoxic medicinal products (see section 4.5).

As with other cytotoxic agents, epirubicin may induce hyperuricaemia as a result of rapid lysis of neoplastic cells. Blood uric acid levels should therefore be checked so that this phenomenon may be recognised and properly managed. Hydration, urine alkalinisation and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumor-lysis syndrome.

Epirubicin is mainly eliminated via the liver. Before starting therapy with epirubicin, and if possible during treatment, liver function should be evaluated (SGOT, SGT, alkaline phosphatase, bilirubin). In patients with decreased liver function, epirubicin clearance can be reduced. For these patients a dose reduction is recommended (see section 4.2).

Serum creatinine levels should be checked regularly prior to and during treatment. For patients with increased serum creatinine (> 5 mg/dl) a dose reduction is proposed (see section 4.2).

Epirubicin may impart a red colour to the urine for one or two days after administration. This medicinal product contains 3.6 mg sodium (0.16 mmol) per ml. To be taken into consideration for patients on a controlled sodium diet.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Epirubicin can be used in combination with other anti-cancer agents but patients should be monitored for additive toxicity, especially myelotoxicity and gastrointestinal toxicity. Drug interactions with epirubicin have been observed with cimetidine, dexverapamil, dexrazoxane, docetaxel, interferon  $\alpha$ 2b, paclitaxel and quinine.

Cimetidine 400 mg b.i.d given prior to epirubicin 100 mg/m<sup>2</sup> 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-deoxydoxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P-450 activity.

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

Prior administration of higher doses (900 mg/m<sup>2</sup> and 1200 mg/m<sup>2</sup>) of dexrazoxane may increase the systemic clearance of epirubicin and result in a decrease in AUC.

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

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

Paclitaxel has been shown to increase plasma concentrations of epirubicin when paclitaxel is administered before epirubicin. When paclitaxel is administered after epirubicin no detectable changes in epirubicin plasma concentrations have been observed. With concomitant use, the latter administration schedule is therefore recommended.

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

The potential risk of cardiotoxicity may increase in patients who have received concomitant cardiotoxic agents (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes), or concomitant (or prior) radiotherapy to the mediastinal area.

If epirubicin is used concomitantly with other drugs that may cause heart failure, e.g. calcium channel blockers, then cardiac function must be monitored throughout the course of treatment.

Epirubicin is mainly metabolised in the liver; each concomitant medication which affects hepatic function can also affect the metabolism or the pharmacokinetics of epirubicin and, consequently, its efficacy and/or toxicity.

This product is generally not recommended in combination with live attenuated vaccines.

#### **4.6 Pregnancy and lactation**

There is no conclusive information as to whether epirubicin may adversely affect human fertility or cause teratogenesis. Experimental data, however, suggest that epirubicin may harm the foetus. Like most other anti-cancer agents, epirubicin has shown mutagenic and carcinogenic properties in animals. Both men and women receiving epirubicin should be informed of the potential risk of adverse effects on reproduction. Women of childbearing potential should be fully informed of the potential hazard to the foetus and the possibility of genetic counselling should be considered if 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 (see section 4.4).

Breastfeeding must be discontinued before and during therapy with epirubicin.

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

There have been no reports of particular adverse events relating to the effects on ability to drive and to use machines.

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

#### **4.8 Undesirable effects**

Adverse event frequencies have been categorised as follows: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

##### *Infections and infestations:*

Fever, infections, pneumonia, sepsis and septic shock may occur as a result of myelosuppression.

##### *Neoplasms benign, malignant and unspecified (including cysts and polyps):*

Rare: secondary acute myeloid leukaemia with or without a pre-leukaemic phase, in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents. These leukaemias have a short (1-3 years) latency.

##### *Blood and lymphatic system disorders:*

Myelosuppression (leucopenia, granulocytopenia, neutropenia, febrile neutropenia, thrombocytopenia, anaemia). Haemorrhage and tissue hypoxia (as a result of myelosuppression) may occur.

High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumours and has caused adverse events which are not different from those seen at conventional doses with the exception of reversible severe neutropenia (< 500 neutrophils/mm<sup>3</sup> for < 7 days) which occurred in the majority of patients. Only few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.

*Immune system disorders:*

Common: allergic reactions following intravesical administration.

Uncommon: sensitivity to light or hypersensitivity in the case of radiotherapy (“recall phenomenon”).

Rare: anaphylaxis (anaphylactic/anaphylactoid reactions with or without shock including skin rash, pruritus, fever and chills).

*Cardiac disorders:*

Rare: cardiotoxicity (ECG changes, tachycardia, arrhythmia, cardiomyopathy, congestive heart failure (dyspnoea, oedema, enlargement of the liver, ascites, pulmonary oedema, pleural effusions, gallop rhythm), ventricular tachycardia, bradycardia, AV block, bundle-branch block (see section 4.4).

*Vascular disorders:*

Uncommon: thrombophlebitis

Coincidental cases of thromboembolic events (including pulmonary embolism [in isolated cases with fatal outcome]) have occurred.

*Gastrointestinal disorders:*

Common: nausea, vomiting, diarrhoea, which can result in dehydration, loss of appetite and abdominal pain. Oesophagitis and hyperpigmentation of the oral mucosa may also occur.

*Skin and subcutaneous tissue disorders:*

Very common: alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males.

Common: hot flushes

Uncommon: hyperpigmentation of skin and nails. Skin reddening.

Rare: urticaria.

*General disorders and administration site conditions:*

Common: mucositis – may appear 5-10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, ulceration and bleeding, mainly along the side of the tongue and the sublingual mucosa.

Common: redness along the infusion vein. Local phlebitis, phlebosclerosis. Local pain and tissue necrosis (following accidental paravenous injection) may occur.

Uncommon: headache

Rare: fever, chills, dizziness, amenorrhoea, azoospermia, hyperuricaemia (as a result of rapid lysis of neoplastic cells). Hyperpyrexia, malaise, weakness and increased transaminase levels have also been reported.

*Injury, poisoning and procedural complications:*

Common: chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration.

#### **4.9 Overdose**

Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 days. Treatment should aim to support the patient during this period and should use such measures as antibiotics, blood transfusion and reverse barrier nursing. Delayed cardiac failure has been seen with the anthracyclines 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. Epirubicin is not dialyzable.

### **5 PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotheapeutic group: Antineoplastic agent. ATC code: L01D B03

Epirubicin is a cytotoxic active antibiotic from the anthracycline group.

The mechanism of action of epirubicin is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin has proved to be active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcomas SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

#### **5.2 Pharmacokinetic properties**

In patients with normal hepatic and renal function, plasma levels after intravenous injection of 60-150 mg/m<sup>2</sup> of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. Between 60 and 120 mg/m<sup>2</sup> there is an extensive linear pharmacokinetic, 150 mg/m<sup>2</sup> is at the margin of dose linearity. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.

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

The 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel than those of the unchanged drug.

Epirubicin is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours.

Biliary excretion represents the major route of elimination, about 40% of the administered dose being recovered in the bile in 72 hours. The drug does not cross the blood brain barrier.

### **5.3 Preclinical safety data**

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

Epirubicin, like other anthracyclines, was mutagenic, genotoxic, embryotoxic and carcinogenic in rats. No malformations were seen in rats or rabbits, but like other anthracyclines and cytotoxic drugs, epirubicin must be considered potentially teratogenic.

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

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium Chloride  
Water for Injections  
Hydrochloric acid for pH adjustment

### **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. Only the diluents detailed in section 6.3 should be used.

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**

Before first opening: 2 years

After dilution: after dilution in Glucose 5% or Sodium Chloride 0.9%, chemical and physical in-use stability has been demonstrated for 60 minutes at +25°C.

From a microbiological point of view, the diluted solution 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°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

#### **6.4 Special precautions for storage**

Store in a refrigerator (2°C – 8°C).

Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

#### **6.5 Nature and contents of container**

5ml, 10 ml, 25 ml, 100 ml type I colourless glass vials, with a bromobutyl rubber stopper and flip-off cap. Box of 1, 5 or 10.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

For methods of administration, see section 4.2.

As with other potentially toxic compounds, caution should be exercised when handling Epirubicin 2 mg/ml, solution for injection. The handling of this cytotoxic agent by nursing or medical personnel requires every precaution to guarantee the protection of the handler and his surroundings.

Epirubicin 2 mg/ml, solution for 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.

## **7 MARKETING AUTHORISATION HOLDER**

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**8     MARKETING AUTHORISATION NUMBER**  
PL 30329/0001

**9     DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
28/08/2008

**10    DATE OF REVISION OF THE TEXT**  
28/08/2008



## **Module 3**

### **Product Information Leaflet**

## PACKAGE LEAFLET: INFORMATION FOR THE USER

### Epirubicin 2 mg/ml, solution for injection Epirubicin hydrochloride

**Read all of this leaflet carefully before you start using this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

#### **In this leaflet:**

1. What Epirubicin is and what it is used for
2. Before you use Epirubicin
3. How to use Epirubicin
4. Possible side effects
5. How to store Epirubicin
6. Further information

## **1. WHAT EPIRUBICIN IS AND WHAT IT IS USED FOR**

Epirubicin is an anti-cancer medicine. Treatment with an anti-cancer medicine is sometimes called cancer chemotherapy.

Epirubicin is used in the treatment of:

- Breast and gastric cancers
- Bladder cancers

Epirubicin is also used to help prevent recurrence of bladder cancer after surgery.

## **2. BEFORE YOU TAKE EPIRUBICIN**

#### **Epirubicin should not be used:**

- if you are hypersensitive (allergic) to epirubicin hydrochloride or similar medicines on previous occasions,
- if your blood cell count is too low. This is measured by healthcare personnel,
- if you have suffered or currently have problems with your heart,
- if you are breastfeeding,
- if you have a severe infection.

When administered intravesically (directly into the bladder), Epirubicin should not be used if:

- the cancer has penetrated the bladder wall,
- you have an infection in your urine,
- you have pain or inflammation in your bladder,
- your doctor has problems inserting a catheter (tube) into your bladder,
- there is a large volume of urine left in your bladder after you attempt to empty it.

#### **Special care will be taken:**

- to ensure the number of cells in your blood does not drop too low. Your doctor will regularly check this,
- if you are experiencing severe inflammation or ulcers in your mouth,
- to check the level of uric acid in your blood. Your doctor will regularly check this,
- if you have liver disease,

- to ensure your heart is working properly. Your doctor will regularly check this,
- if you have received or are receiving radiotherapy to the chest area,
- if you are planning to start a family, whether you are male or female.

### **Taking other medicines**

Please tell your doctor or healthcare personnel if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Epirubicin should not be used:

- if you have been treated with high doses of some other anti-cancer medicines including doxorubicin and daunorubicin which belong to the same group of drugs as epirubicin (called anthracyclines). They have similar side effects (including their effects on the heart)

Special care will be taken if you are taking any of the following medicines:

- other medicines that may affect your heart and/or liver,
- cimetidine (a drug used to reduce the acidity in your stomach),
- paclitaxel and docetaxel (drugs used in some cancers),
- interferon alpha-2b ( a drug used in some cancers and lymphomas and for some forms of hepatitis),
- quinine (drug used for treatment of malaria and for leg cramps),
- dexrazoxane (a drug sometimes used with doxorubicin),
- dexverapamil (a drug used to treat some heart conditions).

This product is generally not recommended in combination with live attenuated vaccines.

### **Pregnancy and breast-feeding**

Epirubicin must not be used if you are pregnant, unless it has been discussed with your doctor, or if you are breast-feeding.

If you become pregnant whilst receiving epirubicin you should inform your doctor immediately.

Both men and women should use effective contraception during treatment with Epirubicin and for 6 months after treatment with epirubicin has finished.

### **Fertility**

Epirubicin can have an anti-fertility effect. Therefore, male patients treated with epirubicin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.

### **Driving and using machines**

You may feel and/or be sick after being given this medicine, therefore special care should be taken when driving or using machines.

### **Important information about some of the ingredients of Epirubicin**

This medicine contains 3.6 mg (0.16 mmol) of sodium per ml. This should be taken into consideration if you are on a controlled sodium diet.

## **3. HOW TO USE EPIRUBICIN**

The dose of medicine given to you will depend on the type of cancer you have, your health, how well your liver is working and any other medicines you may be taking.

The method of administration, like the frequency of administration and duration of treatment, will depend on the route of administration as detailed below:

#### By injection or infusion into a vein

The medicine may be given as an injection into a vein over 3-5 minutes. It may also be diluted with glucose (sugar solution) or sodium chloride (salt water) before it is infused slowly, usually via a drip into a vein over 30 minutes. You may be given another dose of this medicine in 3 weeks.

By injection into the bladder through a tube [“catheter”] (intravesical administration)

The medicine may be given directly into the bladder using a catheter. If this route is used, you should not drink any fluids for 12 hours before treatment so that your urine will not dilute the drug too much. The solution should be kept in your bladder for 1-2 hours after treatment. You will be rotated occasionally to ensure even exposure of all parts of the bladder to the drug.

Care should be taken to ensure that the contents of the bladder, when emptied, do not come into contact with the skin. In case of skin contact, thoroughly wash the affected area with soap and water but do not scrub.

While you are receiving epirubicin your doctor will give you regular blood tests. This is to measure the effect the drug is having. Your doctor will also do regular tests on how your heart is working.

If the injection has been added to a bag of fluid for injection, or for administration to the bladder, it should be labelled with the strength of the drug, volume and the time after which it should not be used.

As this medicine will be given to you whilst you are in hospital it is unlikely that you will be given too little or too much, however, tell your doctor or pharmacist if you have any concerns.

#### **4. POSSIBLE SIDE EFFECTS**

Like all medicines, Epirubicin can have side effects, although not everybody gets them.

**If any of the following happen when epirubicin is given by infusion into a vein, tell your doctor immediately:**

- if there is any redness, pain or swelling at the injection site,
- if you have symptoms of heart problems such as chest pain, shortness of breath, swelling of your ankles (these effects may occur up to several weeks after finishing treatment with epirubicin),
- if you have a severe allergic reaction; symptoms include faintness, skin rash, itching, swelling of the face, difficulty in breathing or wheezing. In some cases collapse may occur.

These are very serious side effects. You may need urgent medical attention.

Other side effects may also be noticed after infusion of epirubicin into a vein.

**If you experience any of the following tell your doctor as soon as possible:**

*Very common side effects (probably affecting more than 1 in 10 patients):*

Loss of hair, normally accompanied by lack of beard growth in males ♦ Decrease in white blood cell count when high doses of epirubicin are given.

*Common side effects (probably affecting more than 1 in 100 patients):*

Allergic reactions ♦ Nausea (feeling sick), vomiting (being sick), diarrhoea, loss of appetite, abdominal pain ♦ Inflammation of the oesophagus ♦ Dark areas (pigmentation) in your mouth ♦ Swelling and/or pain and/or bleeding in your mouth, mainly along the side of the tongue and under the tongue ♦ Hot flushes ♦ Redness and swelling of the vein into which the product is injected, Vein feels hard. Local pain and tissue necrosis (death of cells and living tissue) if the product is accidentally administered outside the vein ♦ Pain on passing urine or a change in frequency of passing urine, sometimes with blood in the urine after injection into the bladder.

*Uncommon side effects (probably affecting less than 1 in 100 patients):*

Sensitivity or hypersensitivity to light ♦ Thrombophlebitis (inflammation of the vein related to a blood clot) ♦ Dark areas (pigmentation) of the skin and nails. Skin reddening ♦ Headache.

*Rare side effects (probably affecting less than 1 in 1000 patients):*

Acute leukaemia (blood cancer) ♦ Severe allergic reactions with or without shock including skin rash, pruritus (itching), fever and chills ♦ Heart problems ♦ Urticaria (nettle rash) ♦ Fever, chills, dizziness ♦

Absence of menstrual periods, reduced or absent sperm in the semen ♦ High levels of uric acid in the blood (indicator of cells destruction) ♦ Generally feeling unwell, weakness ♦ Increased levels of liver enzymes (indicator of liver damage).

*Other side effects (frequency cannot be estimated from the available data):*

Embolism (blockage of a blood vessel) including pulmonary embolism (blood clot in the lungs) ♦ Pneumonia (chest infection), symptoms of an infection due to the lack of white blood cells ♦ Decrease in blood cell count that may lead to bleeding and/or shortage of oxygen in the tissue.

Your urine may be red in colour for a couple of days after being given epirubicin.

Epirubicin may also affect your heart function, liver function and the number of cells in your blood. Your doctor will monitor such effects with regular heart and blood tests.

If epirubicin is injected directly into the bladder (intravesically) you may experience pain or difficulty when passing urine. Blood may also be seen in your urine. If you notice either of these side effects, you should inform your doctor.

When given in combination with other anti-cancer drugs, some patients have developed a secondary leukaemia (cancer of the blood) after completing treatment. This is rare.

If you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

## **5. HOW TO STORE EPIRUBICIN**

Keep out of the reach and sight of children.

The vials will be stored in a refrigerator (2°C – 8°C).

Keep the vial in the outer carton in order to protect from light.

Do not use after the expiry date printed on the vial label and carton.

## **6. FURTHER INFORMATION**

### **What Epirubicin contains**

- The active substance is epirubicin hydrochloride.
- The other ingredients are sodium chloride, water for injections and hydrochloric acid used as a pH adjuster.

### **What Epirubicin looks like and contents of the pack**

Epirubicin is in the form of a solution for injection.

Each millilitre (ml) of solution contains 2 milligrams (mg) of epirubicin hydrochloride. The medicine is presented in glass containers called vials, containing 10 mg (5 ml), 20 mg (10 ml), 50 mg (25 ml), and 200 mg (100 ml) of epirubicin hydrochloride.

The vials are available in packs of 1, 5 or 10 vials of 5 ml, 10ml, 25 ml or 100 ml.

Not all pack sizes may be marketed.

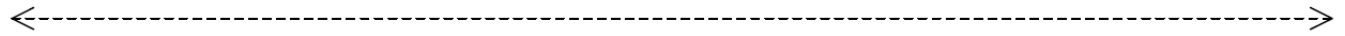
### **Marketing Authorisation Holder**

Merck Generiques SCS  
34 Rue Saint Romain  
69359 Lyon Cedex 08  
France

### **Manufacturer(s)**

Laboratoires Thissen S.A - Rue de la Papyrée 2-6 - B-1420 Braine-l'Alleud – Belgium  
or  
Merck Génériques, 34 rue Saint-Romain - 69359 Lyon Cedex 08 - France

**This leaflet was last approved in <date>**



**The following information is intended for medical or healthcare professionals only:**

For intravenous injection and intravesical administration

### **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. Only the diluents detailed in 'Dilution Instructions' should be used.

Neither the injection nor any diluted solution should be mixed with any other drugs (a physical incompatibility with heparin has been reported).

### **Dilution Instructions**

The injection may be given via the tubing of a free-running intravenous saline infusion. Where the injection is to be administered after dilution, the following instructions should be followed.

Epirubicin may be diluted under aseptic conditions 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 vials should be discarded immediately.

### **Safe Handling**

This is a cytotoxic product, please follow your local policy guidelines for instructions on the safe handling/disposal of cytotoxics.

### **Storage**

Store in a refrigerator (2°C - 8°C).

Keep the vial in the outer carton in order to protect from light.

In use: Epirubicin 2 mg/ml injection may be further diluted as detailed above. The infusion solution is chemically stable when stored in infusion bags prepared under full aseptically controlled conditions for 60 minutes at 25°C. 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 unless dilution has taken place in controlled and validated aseptic conditions.

## Module 4

### Labelling

#### LABELLING

##### BOX

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**1. NAME OF THE MEDICINAL PRODUCT**

Epirubicin 2 mg/ml, solution for injection  
Epirubicin hydrochloride

**2. STATEMENT OF ACTIVE SUBSTANCE**

1 ml of solution for injection contains 2 mg of epirubicin hydrochloride.  
<Each vial contains 10 mg of epirubicin hydrochloride in 5 ml.> or  
<Each vial contains 20 mg of epirubicin hydrochloride in 10 ml.> or  
<Each vial contains 50 mg of epirubicin hydrochloride in 25 ml.> or  
<Each vial contains 200 mg of epirubicin hydrochloride in 100 ml.>

**3. LIST OF EXCIPIENTS**

Sodium chloride, water for injections, hydrochloric acid.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection.  
<Vial of 5 ml. Box of<1 or 5 or 10>.> or  
<Vial of 10 ml. Box of<1 or 5 or 10>.> or  
<Vial of 25 ml. Box of<1 or 5 or 10>.> or  
<Vial of 100 ml. Box of<1 or 5 or 10>.>

**5. METHOD AND ROUTE OF ADMINISTRATION**

Intravenous or intravesical use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Read the package leaflet before use.

**8. EXPIRY DATE**

Exp. MM/YYYY

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Keep the vial in the outer carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

All items used for preparation, administration or otherwise coming into contact with epirubicin should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Generiques SCS  
34 Rue Saint Romain  
69359 Lyon Cedex 08  
France

**12. MARKETING AUTHORISATION NUMBER(S)**

PL 30329/0001

**13. BATCH NUMBER**

Batch number:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

POM

**15. INSTRUCTIONS ON USE**

Not applicable.

**16. INFORMATION IN BRAILLE**

Not applicable.



## IMMEDIATE PACKAGING UNITS

### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

#### 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Epirubicin 2 mg/ml, solution for injection  
Epirubicin hydrochloride  
Intravenous or intravesical use.

#### 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

#### 3. EXPIRY DATE

Exp. MM/AAAA

#### 4. BATCH NUMBER

Batch number:

#### 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

<Each vial contains 10 mg of epirubicin hydrochloride in 5 ml.> or  
<Each vial contains 20 mg of epirubicin hydrochloride in 10 ml.> or  
<Each vial contains 50 mg of epirubicin hydrochloride in 25 ml.> or  
<Each vial contains 200 mg of epirubicin hydrochloride in 100 ml.>  
Box of <1 or 5 or 10> vials.

#### 6. OTHER

Store in a refrigerator.  
Keep the vial in the outer carton in order to protect from light.

## Module 5

### Scientific discussion during initial procedure

#### RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Epirubicin 2 mg/ml, solution for injection (UK/H/1033/001/DC), in the treatment of a range of neoplastic conditions, including breast and gastric carcinomas and (when administered intravesically) papillary transitional cell carcinoma of the bladder; carcinoma-in-situ; and prophylaxis of recurrences after transurethral resection, could be approved.

#### EXECUTIVE SUMMARY

##### Problem statement

This abridged decentralised application concerns a generic version of epirubicin 2 mg/ml, solution for injection submitted under Article 10.1 of Directive 2001/83/EC. The reference product is Farmorubicin 2 mg/ml, solution for injection, authorised to Pfizer ApS, Denmark on 28 June 1985. Hence the 10 year rule is fulfilled and the legal basis of this application is satisfactory.

With the UK as the Reference Member State in this Decentralised Procedure, Merck Generiques SCS applied for a Marketing Authorisation for Epirubicin 2 mg/ml, solution for injection in Austria, Belgium, Denmark, Greece, Finland, Norway, Portugal, Sweden and the Slovak Republic.

##### About the product

Epirubicin - a 4'-epimer of doxorubicin - is an oncolytic drug of the anthracycline group. As in the case of other anthracyclines, the precise mechanism of action of epirubicin is unknown, but is primarily related to intercalation of the planar ring with DNA and subsequent inhibition of DNA and RNA synthesis. Epirubicin appears to be less cardiotoxic than doxorubicin. Epirubicin is indicated for the treatment of a wide range of tumours.

The proposed indications are:

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

- Breast and gastric carcinomas,

When administered intravesically, epirubicin has been shown to be beneficial in the treatment of:

- Papillary transitional cell carcinoma of the bladder,
- Carcinoma-in-situ,
- Prophylaxis of recurrences after transurethral resection.

##### General comments on the submitted dossier

The submitted dossier is of an adequate standard.

##### General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products. The RMS has accepted copies of current manufacturer authorisations issued by inspection services of

the competent authorities as certification that acceptable standards of GMP are in place at this site. Since a literature review has been presented for the nonclinical / clinical overviews, it is not known whether the studies cited were conducted in accordance with the GLP / GCP regulations. However, it is assumed that the studies conducted by the innovator would have been in compliance with the standards prevailing at the time.

## **SCIENTIFIC OVERVIEW AND DISCUSSION**

### **Quality aspects**

The chemical-pharmaceutical documentation in relation to Epirubicin 2 mg/ml, solution for injection is of sufficient quality in view of present European regulatory requirements.

### **Active substance**

The control tests and specifications for the active substance are adequately drawn up. Stability studies have been performed with the active substance. No significant changes in any parameters were observed. The proposed retest period of 2 years is justified.

### **Drug Product**

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed and the results show that the finished product meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for the drug product are adequately drawn up. The proposed shelf-life of 2 years is considered acceptable. After dilution in glucose 5% or sodium chloride 0.9%, chemical and physical in-use stability has been demonstrated for 60 minutes at +25°C. However, from a microbiological point of view, the diluted solution 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°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

### **Non-clinical aspects**

The pharmacodynamic, pharmacokinetic and toxicological properties of epirubicin are well known. As epirubicin is a widely used, well-known active substance, the applicant has not provided additional studies and these are not required. An overview based on a literature review is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is satisfactory.

### **Clinical aspects**

#### **Pharmacokinetics (PK)**

No novel PK data are supplied. The PK claims within the SPC are appropriately consistent with the innovator label. The product proposed for marketing authorisation is an aqueous solution intended for intravenous and intravesical administration containing the same active substance in the same concentration as the currently authorised product. According to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) no bioequivalence studies are required for parenterally administered aqueous solutions.

**Pharmacodynamics (PD)**

No novel efficacy or safety data are supplied or required for this application. The PD claims within the SPC are appropriately consistent with the UK innovator label.

**Clinical efficacy**

No novel efficacy data are supplied or required for this generic application, thus the efficacy claims within the SPC are appropriately consistent with the UK innovator label.

**Clinical safety**

No new safety data have been submitted and none are required for this application, hence the SPC claims are appropriate.

**BENEFIT RISK ASSESSMENT**

The risk: benefit ratio for this product is considered favourable and approval is recommended.

## **Overall conclusion**

### **QUALITY**

The important quality characteristics of Epirubicin 2 mg/ml, solution for injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### **PRECLINICAL**

No preclinical data is needed for this application.

No new or unexpected safety concerns arise from this application.

### **EFFICACY**

Clinical studies have demonstrated the efficacy of Epirubicin 2 mg/ml, solution for injection in the treatment of a range of neoplastic conditions.

The product literature is satisfactory and consistent with that for the innovator product.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.