

# **Public Assessment Report**

## **Decentralised**

**Epirubicin Hydrochloride 2mg/ml solution for injection or  
infusion**

**Epirubicin hydrochloride**

**UK/H/1123/01//DC**

**Accord Healthcare Ltd**

## LAY SUMMARY

The MHRA granted Accord Healthcare Ltd a Marketing Authorisation (licence) for the medicinal product Epirubicin hydrochloride 2mg/ml solution for injection or infusion on 19/02/2009. The product contains the active ingredient epirubicin hydrochloride and is used to treat some forms of cancer including breast carcinoma, gastric cancer and bladder cancer. The product is a prescription only medicine.

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## Module 1

<b>Product Name</b>	Epirubicin hydrochloride 2 mg/mL Solution for Injection or infusion
<b>Type of Application</b>	Standard Abridged Decentralised (Article 10.1)
<b>Active Substance (INN)</b>	Epirubicin hydrochloride
<b>Pharmacotherapeutic Classification (ATC)</b>	Anthracyclines and related substances (L01DB03)
<b>Pharmaceutical Form and Strength</b>	Solution for injection or infusion, 2 mg/mL
<b>Procedure Number</b>	<b>UK/H/1123/01/DC</b>
<b>RMS</b>	UK
<b>CMS</b>	AT, BE, CZ, DE, DK, EE, ES, FI, HU, IE, IT, LT, LV, NL, NO, PL, PT, SE, SK
<b>Start Date</b>	01/05/2007
<b>End Date</b>	19/02/2009
<b>MA Number</b>	PL 20075/0024
<b>Name and address of MA holder</b>	<b>Accord Healthcare limited</b> Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, UK

## Module 2

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Epirubicin Hydrochloride 2 mg/ml solution for injection or infusion

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2 mg epirubicin hydrochloride.

Each 5/10/25/100 ml vial contains 10/20/50/200 mg epirubicin hydrochloride.

Excipient: Contains sodium 3.54 mg/ml (0.154 mmol).

For a full list of excipients, see section 6.1

#### 3 PHARMACEUTICAL FORM

Solution for injection or infusion

A clear red solution

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

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

- Carcinoma of the breast
- Gastric cancer

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.
- 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.

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 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 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***

Epirubicin 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/m<sup>2</sup> day 1, every 3 weeks.

For high dose treatment, epirubicin 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 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 (in accordance with local guidelines) 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:

Cancer Indication	Epirubicin Dose (mg/m <sup>2</sup> ) <sup>a</sup>	
	Monotherapy	Combination Therapy
Ovarian cancer	60–90	50–100
Gastric cancer	60–90	50
SCLC	120	120
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

**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. In establishing the maximal cumulative doses of Epirubicin (usually: 720 – 1000 mg/m<sup>2</sup>), any concomitant therapy with potentially cardiotoxic drugs should be taken into account.

**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		50%
> 3 mg/100 ml	> 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. Lower starting doses should be considered in patients with severe renal impairment (serum creatinine >450µmol/l).

**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 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- 2 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 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 to the mediastinal pericardial area and/or who are under medical treatment with potentially cardiotoxic medicinal products (see section 4.5).
- Patients treated with maximal cumulative doses of other anthracyclines such as doxorubicin or daunorubicin.
- Patients with current or previous history of cardiac impairment and myocardial infarction.
- Acute systemic infections.
- Severe liver impairment.
- Severe mucositis of the mouth, pharynx, oesophagus, and gastro-intestinal tract.
- Breast-feeding.

Epirubicin is contraindicated for intravesical administration in case of:

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

Epirubicin can have genotoxic effects. Therefore male patients treated with epirubicin are advised not to take part in conception during and up to 6 months after treatment and to seek advice regarding conservation of sperm prior to treatment because of the possibility of infertility due to therapy with epirubicin. Female patients should not become pregnant during treatment with epirubicin. Male and female should use an effective method of contraception during treatment and for 6 months thereafter.

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

### 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 for 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 take part in conception during and up to 6 months after treatment and to seek advice regarding conservation of sperm prior to treatment because of the possibility of infertility due to therapy with epirubicin.

Female patients should not become pregnant during treatment with epirubicin. Male and female should use an effective method of contraception during treatment and for 6 months thereafter.



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 10th and 14th day, values should return to normal by the 21st 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.

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 such as ECG, echocardiography and, if necessary, measurement of ejection fraction by radionuclide angiography.

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 in a medical treatment with potential cardiotoxic agents (see section 4.5).

Before commencing therapy with epirubicin, and if possible during treatment, liver function should be evaluated (SGOT, SGT, alkaline phosphatase, bilirubin). (see section 4.2) For patients with reduced renal function serum creatinine levels should be checked regularly prior to and during treatment. For patients with increased serum creatinine ( $> 450$  μmol/l) a dose reduction should be considered (see section 4.2).

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.

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

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

Epirubicin can be used in combination with other anticancer agents but patients should be monitored for additive toxicity, especially myelotoxicity and gastrointestinal toxicity. Concomitant use of other medicinal products that may be cardiotoxic or affect cardiac function should be monitored throughout treatment. 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.

Drug interactions with epirubicin have been observed with cimetidine, dexverapamil, dexrazoxane, docetaxel, interferon  $\alpha_2b$ , paclitaxel and quinine.

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

Prior to 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 half life and the total clearance of epirubicin.

Paclitaxel may affect the pharmacokinetics of epirubicin and its metabolite, epirubicinol. In one study, haematological toxicity was greater when paclitaxel was administered before epirubicin compared with after epirubicin. One study has shown that paclitaxel clearance is reduced by 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.

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-deoxy-doxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P-450 activity. Epirubicin used in combination with other cytotoxic agents may result in additive myelotoxicity.

The possibility of a marked disturbance of haematopoiesis needs to be kept in mind with a (pre-) treatment with agents which influence the bone marrow (i.e. cytostatic agents, sulphonamide, cloramphenicol, diphenylhydantoin, amidopyrinedervatives, 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 concomitant with other agents that may cause heart failure, e.g. calcium channel blockers, the cardiac function must be monitored throughout the course of treatment.

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

This medicinal 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 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.

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

It is unknown whether epirubicin is excreted in human breastmilk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment 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 the ability to drive or operate machines.

#### **4.8 Undesirable effects**

*The estimation of frequency:* Very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) not known (cannot be estimated from the available data).

##### ***Investigations***

*Rare:* Increased transaminase levels.

##### ***Cardiac disorders***

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

##### ***Blood and lymphatic system disorder***

*Frequency unknown:* Myelosuppression (leukopenia, granulocytopenia, neutropenia, febrile neutropenia, thrombocytopenia, anaemia), Hemorrhagia 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 have caused adverse events which are no 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.

*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.

#### ***Metabolism and nutrition disorders***

*Rare:* Hyperuricaemia (as a result of rapid lysis of neoplastic cells).

#### ***Infections and infestations***

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

#### ***Injury, poisoning and procedural complications***

*Common:* Chemical cystitis, in some cases haemorrhagic, is observed following intravesical administration.

#### ***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 leukaemia's have short (1-3 years) latency.

#### ***Vascular disorders***

*Uncommon:* Thrombophlebitis.

*Frequency unknown:* Coincidental cases of thromboembolic events (including pulmonary embolism (in isolated cases with fatal outcome)) have occurred.

#### ***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 bleedings, mainly along the side of the tongue and the sublingual mucosa.

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

*Uncommon:* Headache.

*Rare:* Fever, chills, dizziness, hyperpyrexia, malaise, weakness.

#### ***Immune system disorders***

*Common:* Allergic reactions after intravesical administration.

*Uncommon:* Photosensitivity or hypersensitivity in case of radiotherapy ("recall phenomenon").

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

#### ***Reproductive system and breast disorders***

*Rare:* Amenorrhea, azoospermi.

## **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 utilise such measures as 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

Pharmacotherapeutic group: Anthracyclines and related substances 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 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. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.

In a pharmacokinetic study of patients with carcinoma in situ in the bladder the plasma levels of epirubicin after intravesical administration are typically low (<10 ng/ml). A significant systemic resorption is therefore not presumed. In patients with mucous membrane lesions in the bladder (e.g. tumour, cystitis, operations) an increased resorption rate may 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 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 Injections

### 6.2 Incompatibilities

Prolonged contact of the medicinal product with any solution of alkaline pH (including sodium bicarbonate solutions) should be avoided; this will result in hydrolysis (degradation) of the active substance. Only the diluents detailed in section 6.6 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

Shelf life of the product as package for sale:

2 years.

Shelf life after first opening the container:

The vials are for single use only and any unused portion must be discarded after use. From a microbiological point of view, the product should be used immediately after the first penetration of the rubber stopper. If not used immediately, in use storage times and conditions are the responsibility of the user.

Shelf life after dilution of the solution for injection:

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. From a microbiological point of view, 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 not normally be longer than 24 hours at 2-8°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). Do not freeze.

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

For storage after dilution, see section 6.3.

### 6.5 Nature and contents of container

5 and 10 ml vials: Type I tubular glass vial with Teflon-coated rubber stopper and aluminium flip-off white seal

25 ml vial: Type I tubular glass vial with Teflon-coated rubber stopper and aluminium flip-off white/royal blue seal.

100 ml vial: Type I clear moulded glass vial with Teflon-coated rubber stopper and aluminium flip-off white / royal blue seal.

Pack size: 1 vial.

Not all pack sizes may be marketed

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

Epirubicin Hydrochloride 2 mg/ml Injection may be further diluted in Glucose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. For information on the stability of the infusion solutions, please refer to section 6.3.

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

### **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**

Accord Healthcare Limited,  
Sage House, 319, Pinner Road,  
North Harrow,  
Middlesex, HA1 4HF,  
UK

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 20075/0024

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

19/02/2009

## **10 DATE OF REVISION OF THE TEXT**

19/02/2009

## Module 3

# Product Information Leaflet

<p style="text-align: center;"><b>accord</b></p> <p style="text-align: center;">PATIENT INFORMATION LEAFLET</p> <p style="text-align: center;"><b>Epirubicin Hydrochloride</b> <b>2 mg/ml solution for injection</b> <b>or infusion</b> Epirubicin Hydrochloride</p> <p>Read all of this leaflet carefully before you start given this medicine.</p> <ul style="list-style-type: none"> <li>Keep this leaflet. You may need to read it again.</li> <li>If you have further questions, please ask your doctor.</li> <li>This medicine has been prescribed for you do not pass it on to others. It may harm them, even if their symptoms are the same as yours.</li> <li>If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.</li> </ul> <p><b>In this leaflet:</b></p> <ol style="list-style-type: none"> <li>1. What Epirubicin Hydrochloride Injection is and what it is used for</li> <li>2. Before you use Epirubicin Hydrochloride Injection</li> <li>3. How to use Epirubicin Hydrochloride Injection</li> <li>4. Possible side effects</li> <li>5. How to store Epirubicin Hydrochloride Injection</li> <li>6. Further information</li> </ol> <p><b>1. What Epirubicin Hydrochloride Injection is and what it is used for</b></p> <p>The name of your medicine is 'Epirubicin Hydrochloride 2 mg/ml solution for injection or infusion' but in the rest of the leaflet it will be called 'Epirubicin Hydrochloride Injection'.</p> <p><b>What Epirubicin Hydrochloride Injection is</b></p> <p>Epirubicin Hydrochloride Injection is an anti-cancer medicine. Treatment with an anti-cancer medicine is sometimes called cancer chemotherapy. Epirubicin Hydrochloride Injection is part of a group of medicines called anthracyclines. These act upon cells that are actively growing, to slow or stop their growth and increase the chance that the cells die.</p> <p><b>What Epirubicin Hydrochloride Injection is used for</b></p> <p>Epirubicin Hydrochloride Injection is used to treat a variety of cancers. The way in which it is used depends upon the type of cancer that is being treated.</p>	<p>Epirubicin Hydrochloride Injection is used in the treatment of</p> <ul style="list-style-type: none"> <li>Carcinoma of the breast</li> <li>Gastric cancer</li> </ul> <p>When injected into the bladder through a tube, Epirubicin Hydrochloride Injection is used to treat cancer of the bladder wall. It can also be used after other treatments for prevention of such cells from growing again.</p> <p><b>2. Before you use Epirubicin Hydrochloride Injection</b></p> <p><b>Do not use Epirubicin Hydrochloride Injection if you</b></p> <ul style="list-style-type: none"> <li>are allergic (hypersensitive) to epirubicin hydrochloride or any of the other ingredients of Epirubicin Hydrochloride Injection</li> <li>are aware your blood counts are low, as Epirubicin Hydrochloride Injection can lower them further.</li> <li>suffer with or have suffered with severe heart failure</li> <li>suffer from an acute severe infection</li> <li>have severe inflammation in the mouth, pharynx, oesophagus and gastro-intestinal tract</li> <li>are breast-feeding.</li> <li>Severe liver problems</li> </ul> <p>Tell your doctor or hospital pharmacist if any of the above applies to you. In any of the above cases, you should not be given Epirubicin Injection.</p> <p>Epirubicin Hydrochloride Injection should not be injected into the bladder if:</p> <ul style="list-style-type: none"> <li>you suffer from urinary infection</li> <li>there are tumours which penetrate the bladder</li> <li>there are problems placing the tube</li> <li>you have an inflammation of the bladder</li> <li>you have large volume of urine left in your bladder after you attempt to empty</li> <li>your bladder is contracted.</li> </ul> <p>Take special care with Epirubicin Hydrochloride Injection if you</p> <ul style="list-style-type: none"> <li>have some kidney or liver problems. You should inform your doctor before treatment, as he/she needs to take special care.</li> <li>Your doctor will also be making regular checks</li> <li>so that your blood cell counts will not be too low</li> <li>to control the levels of uric acid in the blood</li> <li>to see that your heart and liver are working normally</li> <li>if you have or are to have radiotherapy to the area around the heart.</li> </ul> <p>You should inform your doctor in case you experience swelling and pain in your mouth or mucous membrane.</p> <p>It is possible that the urine will have a red colour for one or two days after administration.</p>	<p><b>Using other medicines</b></p> <p>Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Especially:</p> <ul style="list-style-type: none"> <li>Cimetidine (used to reduce the acid in the stomach).</li> <li>Paclitaxel and docetaxel (used in some cancers).</li> <li>Interferon alfa-2b (used in some cancers and lymphoma and for some yellow fever).</li> <li>Quinine (used for treatment of malaria and for leg cramps).</li> <li>Doxrazoxane (sometimes used with doxorubicin in order to decrease the risk of heart problems).</li> <li>Dexverapamil (used to treat some heart conditions).</li> <li>Other medicines that may affect your liver and/or heart.</li> <li>Live vaccines.</li> </ul> <p>Other medicines that may affect the bone marrow (such as other medicines to treat cancer; sulphonamide and cloramphenicol (antibacterial medicines), diphenylhydantoin (antiepileptic), amikopyrine derivatives (some medicines to treat e.g. pain and fever) and some antiviral medicines).</p> <p><b>Pregnancy and breast-feeding</b></p> <p>Epirubicin Hydrochloride Injection may cause birth defects when used during pregnancy, it is important to tell your doctor if you are pregnant or if you become pregnant during treatment. You must not use Epirubicin Hydrochloride Injection during pregnancy unless clearly indicated by your doctor.</p> <p>If you or your partner are being treated with Epirubicin Hydrochloride Injection effective birth control to prevent pregnancy during treatment and for 6 months after treatment is advised. If pregnancy occurs during treatment, genetic counselling is recommended.</p> <p>There is a risk of sterility due to therapy with Epirubicin Hydrochloride Injection. Male patients should consider storage of sperm before treatment.</p> <p>Epirubicin Hydrochloride Injection may be harmful to nursing infants, therefore women must stop breast-feeding before starting treatment with Epirubicin Hydrochloride Injection.</p> <p><b>Driving and using machines</b></p> <p>Epirubicin Hydrochloride Injection may cause episodes of nausea and vomiting, which can temporarily lead to an impairment of the ability to drive or use machines.</p> <p><b>Important information about some of the ingredients of Epirubicin Hydrochloride Injection</b></p> <p>This medicinal contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially 'sodium free'.</p>
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### 3. How to take Epirubicin Hydrochloride Injection?

Epirubicin Hydrochloride Injection will be given to you by a doctor or nurse, either into a vein or directly into your bladder. Your doctor will decide the correct dose and number of days treatment you receive, this will depend on the type of cancer you have, your health, height, weight, how well your liver is working and any other treatment you may receive.

**By injection or infusion into a vein**  
Epirubicin Hydrochloride Injection may be given as an injection into a vein over 3-5 minutes. It may also be diluted before it is infused slowly, usually via a drip into a vein over 30 minutes.

**By being put into the bladder**

If the injection is given into the bladder, 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 installation. You will need to turn occasionally to make sure all parts of the bladder are exposed 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.

Your doctor will regularly check your blood for any unwanted effects. To detect any possible heart damage your doctor will also monitor your heart for several weeks after the treatment.

**If you receive more Epirubicin Hydrochloride Injection than you should:**

You may notice sores in your mouth, however 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. Please tell your doctor if you have any concerns.

### 4. Possible side effects

Like all medicines, Epirubicin hydrochloride Injection can cause side effects, although not everybody gets them.

If any of the following side effects happen when epirubicin is given by infusion into a vein tell your doctor immediately, as these are very serious side effects. You may need urgent medical attention:

- redness, pain or swelling at the injection site; tissue damage may occur after accidental injection outside a vein
- 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)

- severe allergic reaction, symptoms include faintness, skin rash, swelling of the face and difficulty in breathing or wheeze. In some cases collapse may occur.

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

**Very common (occur in more than 1 in 10 people):**

Hair loss, reduced growth of beard hair.

**Common (occur in less than 1 in 10 people):**

Allergic reactions, feeling or being sick, diarrhoea (which can result in dehydration), loss of appetite, abdominal pain, inflammation of the gullet (oesophagitis), high levels of pigments in the mouth, swelling and pain in your mouth, ulcers involving the lips and/or tongue and/or under the tongue, hot flushes, changes in blood cells causing bleeding, fever or infections.

**Uncommon (occur in less than 1 in 100 people):**

Headache, high levels of pigments in the skin and nails, skin redness, sensitivity to light (in case of radiotherapy), vein inflammation including blood clotting (thrombophlebitis).

**Rare (occur in less than 1 in every 1,000 people):**

Hives (urticaria), fever and/or chills, dizziness, absence of menstrual periods (amenorrhoea), lack of sperm, gout, changes in heart or liver function.

Your urine may be red in colour for a couple of days after being given epirubicin, which is a normal occurrence related to the colour of the medicine.

Longterm effect is a certain type of leukaemia (acute myeloid leukaemia), which has been rarely reported.

If epirubicin hydrochloride is injected directly into the bladder you may experience pain or difficulty when passing urine. Blood may also be seen in your urine.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### 5. How to store Epirubicin Hydrochloride Injection

Store in a refrigerator (2°C-8°C). Do not freeze.

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

Always keep Epirubicin Hydrochloride Injection in a safe place and out of the reach and sight of children.

Do not use Epirubicin Hydrochloride Injection after the expiry date, which is printed on the label and carton after EXP. The expiry date refers to the last day of that month.

Do not use Epirubicin Hydrochloride Injection if you notice any visible signs of deterioration.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

### 6. Further information

**What Epirubicin Hydrochloride Injection contains:**

The active ingredient in Epirubicin Injection is Epirubicin Hydrochloride. Each ml contains 2 mg Epirubicin Hydrochloride.

Other ingredients include sodium chloride, hydrochloric acid and water for injection.

**What Epirubicin Hydrochloride Injection looks like and content of the pack:**

Epirubicin Injection is a clear, red coloured solution.

**Pack sizes:**

1 x 5 ml vial (10 mg/5 ml)

1 x 10 ml vial (20 mg/10 ml)

1 x 25 ml vial (50 mg/25 ml)

1 x 100 ml vial (200 mg/100 ml)

5 and 10 ml vials: Type I tubular glass vial with Teflon-coated rubber stopper and aluminium flip-off white seal

25 ml vial: Type I tubular glass vial with Teflon-coated rubber stopper and aluminium flip-off white/royal blue seal.

100 ml vial: Type I clear moulded glass vial with Teflon-coated rubber stopper and aluminium flip-off white/royal blue seal.

Pack size: 1 vial.

Not all pack sizes may be marketed

**Product license holder:**

Accord Healthcare Limited,

Sage House,

319 Pinner Road,

North Harrow, Middlesex, HA1 4HF,

UK

**Manufacturer:**

Cemlog BRS Ltd,

2040 Budaors, Vasut u.2. Hungary

This leaflet was last approved in 02/2009.

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

**Incompatibilities**

Prolonged contact with any solution of an alkaline pH (including bicarbonate containing solutions) should be avoided as it will result in hydrolysis of the drug. Only the diluents detailed in "Instructions for use" 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.

**Instructions for use**

**Intravenous administration:** It is advisable to administer Epirubicin Hydrochloride Injection via the tubing of a freely flowing intravenous infusion (0.9% sodium chloride). To minimize the risk of thrombosis or perivenous extravasation, the usual infusion times range between 3 and 20 minutes depending upon dosage and volume of the infusion solution.

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.

**Intravesical administration:** Epirubicin Hydrochloride Injection should be diluted in sterile water for injection or 0.9% sterile saline solution before administration. Epirubicin should be instilled using a catheter and retained intravesically for 1-2 hours. During instillation, the patient should be rotated to ensure that the vesical mucosa of the pelvis receives the most extensive contact with the solution. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. The patient should be instructed to void at the end of the instillation.

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.

**Storage**

**Product as package for sale:** Store in a refrigerator (2°C-8°C). Do not freeze. Keep vial in the outer carton in order to protect from light.

**Shelf life after first opening the container:**

The vials are for single use only and any unused portion must be discarded after use. From a microbiological point of view, the product should be used immediately after the first penetration of the rubber stopper. If not used immediately, in use storage times and conditions are the responsibility of the user.

**Shelf life after dilution of the solution for injection:**

The product may be further diluted, under aseptic conditions, in Glucose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. From a microbiological point of view, 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 not normally be longer than 24 hours at 2°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

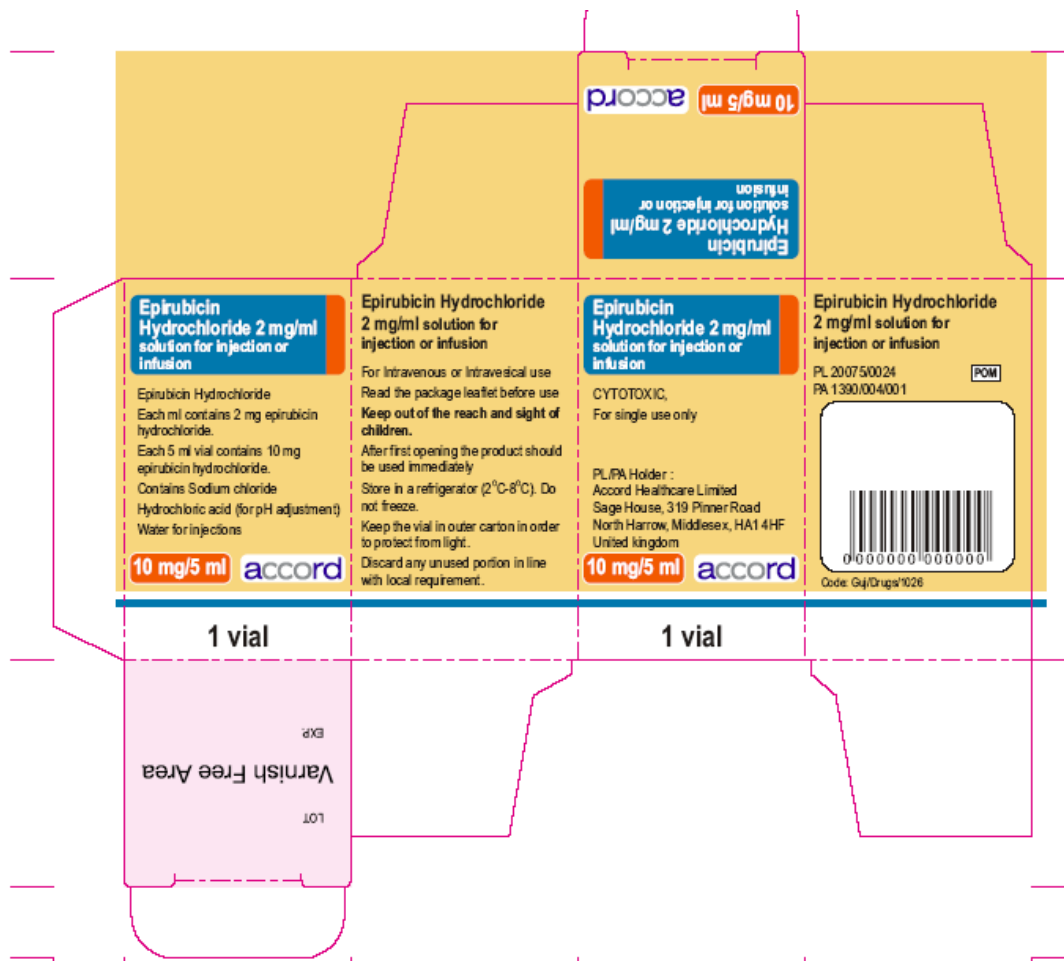
**Disposal**

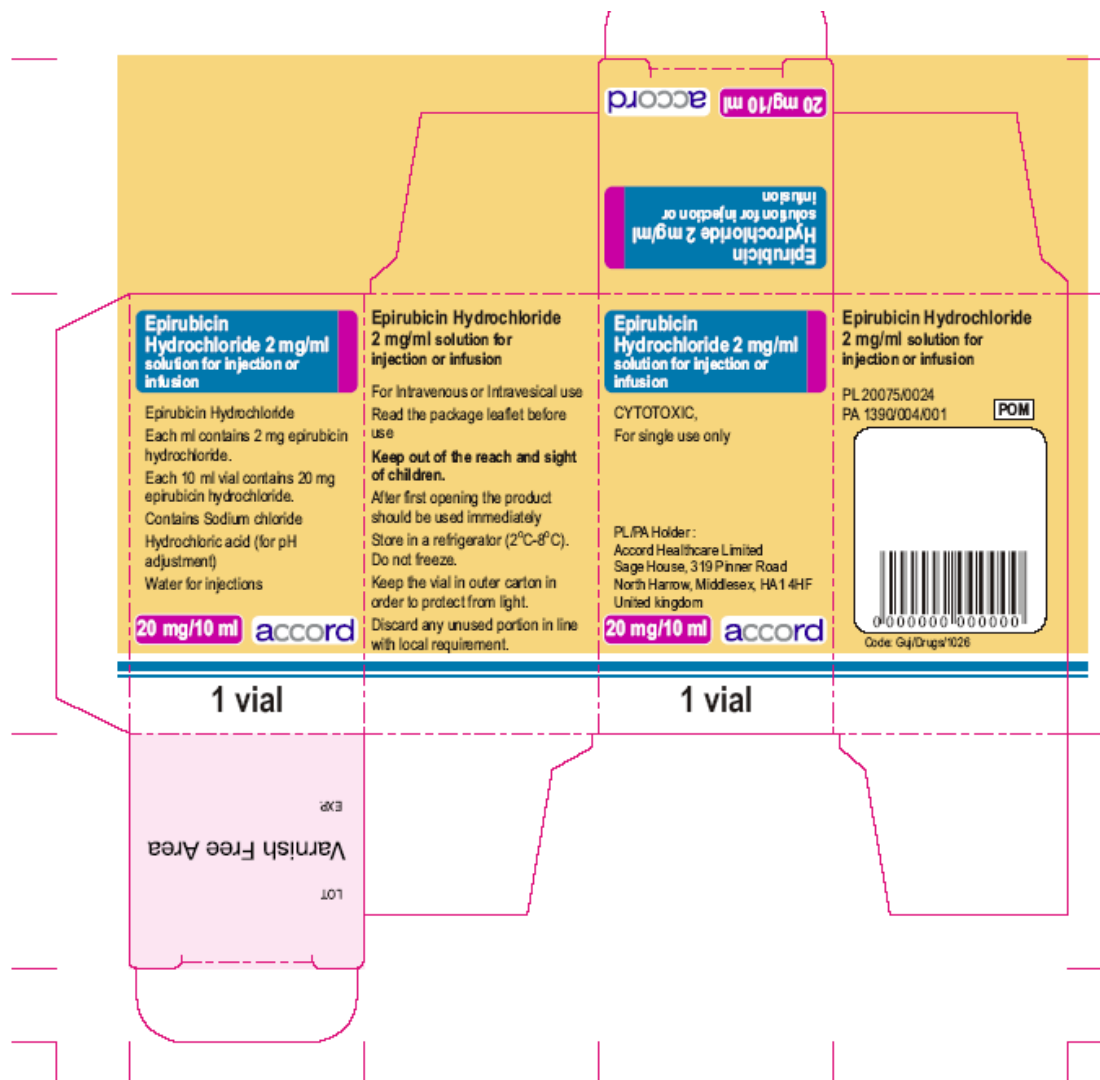
Medicines should not be disposed of via wastewater or household waste. All material used for preparation, administration or otherwise coming into contact with Epirubicin should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

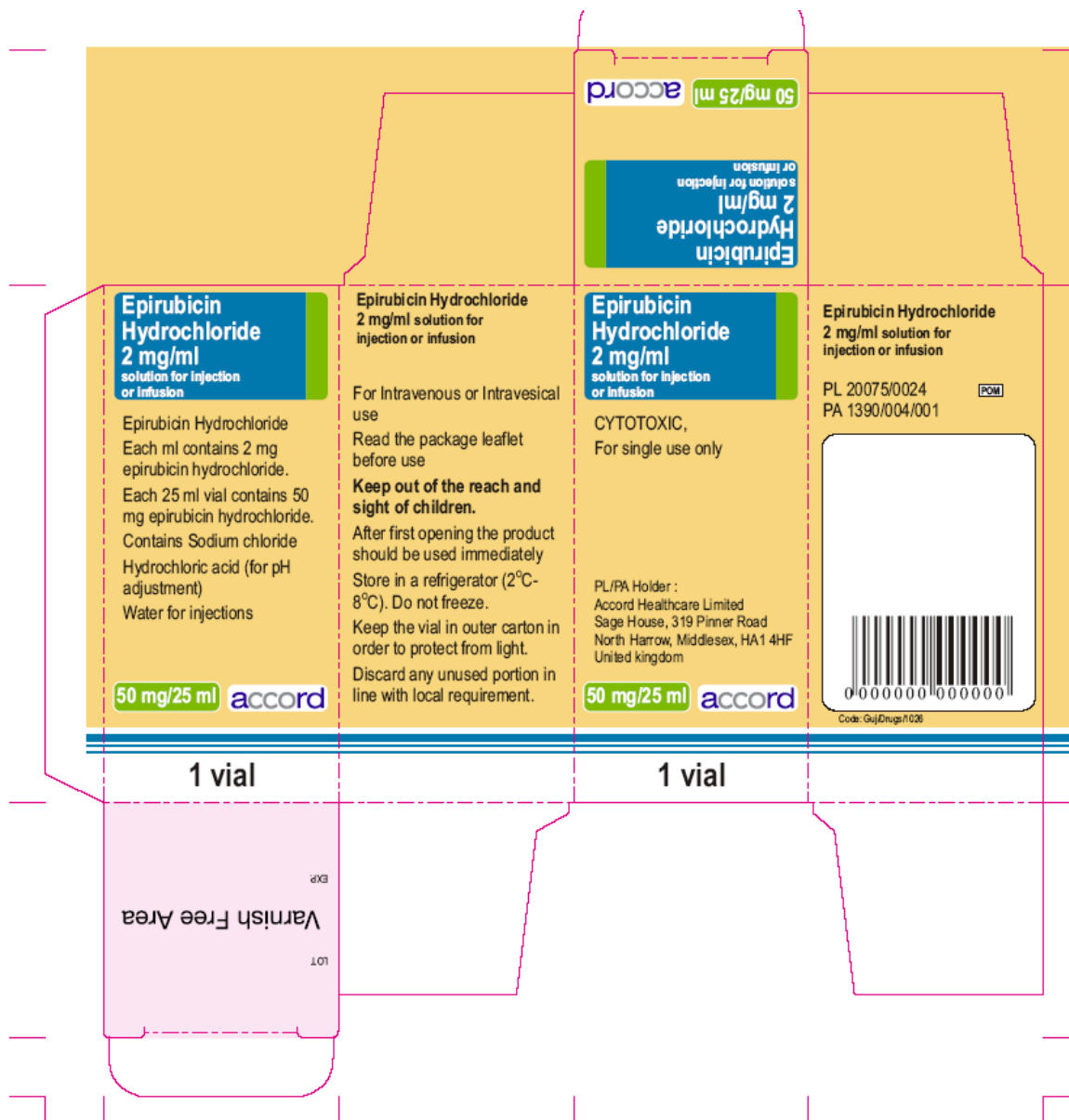
**Please refer to the Summary of Product Characteristics (SPC) for further information about Epirubicin Hydrochloride Injection 2 mg/ml solution for injection or infusion.**

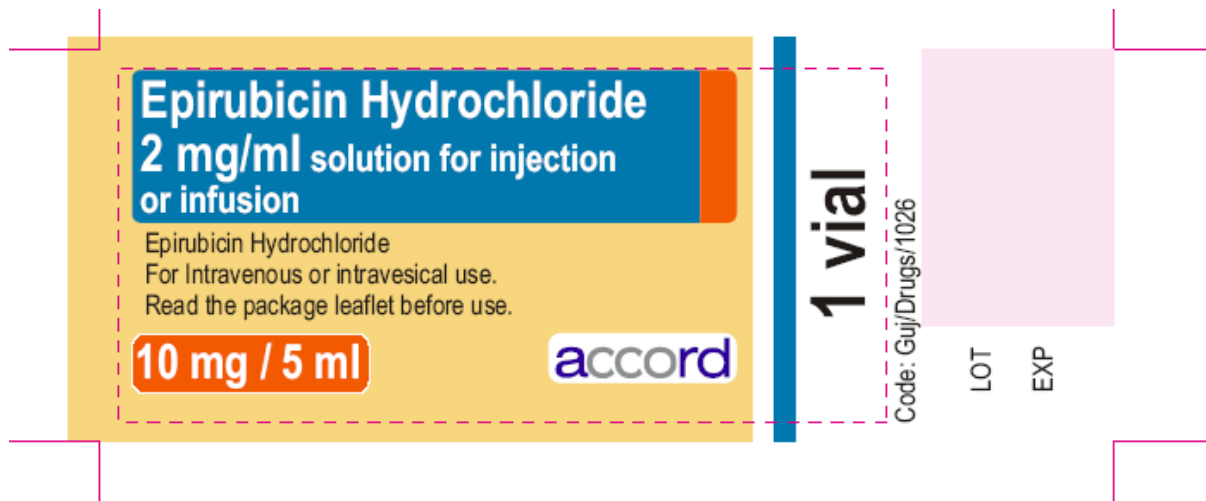
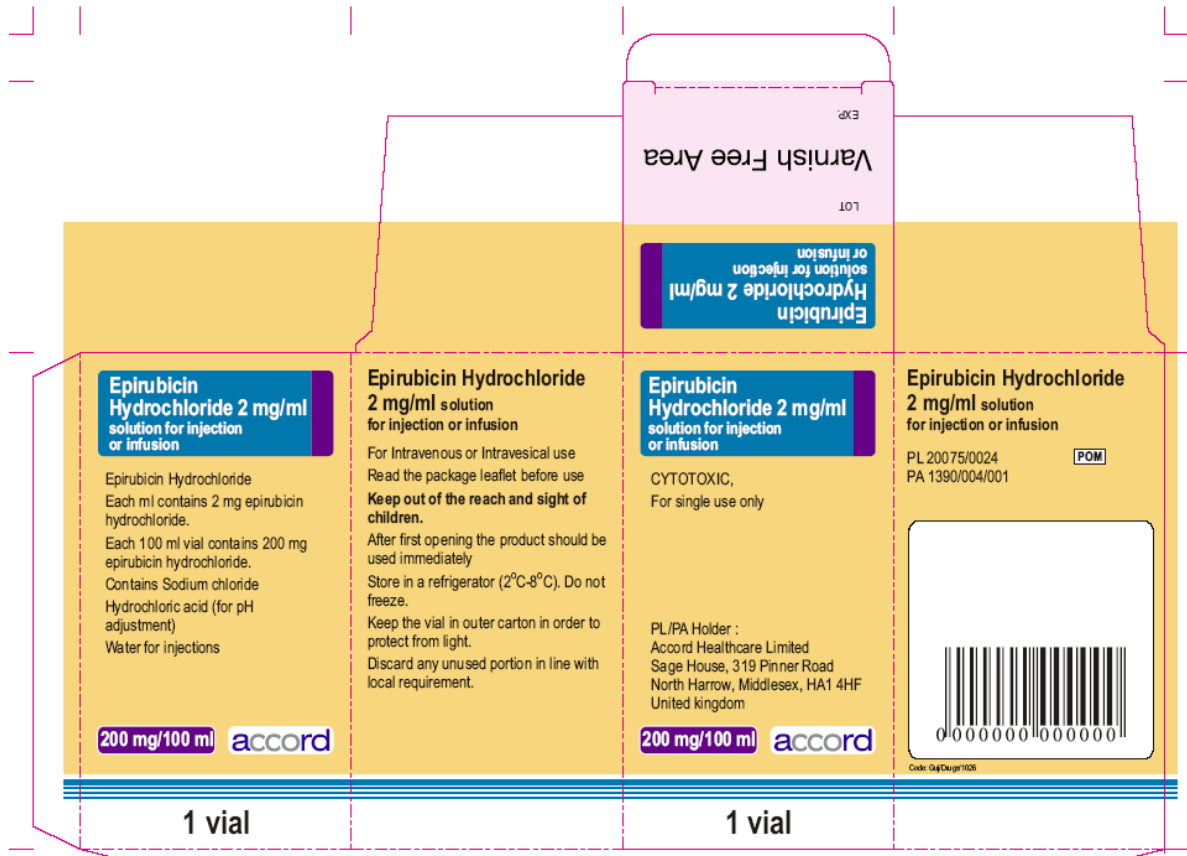
# Module 4

## Labelling









**Epirubicin Hydrochloride**  
**2 mg/ml solution for injection or infusion**

Epirubicin Hydrochloride  
For Intravenous or intravesical use  
Read the package leaflet before use.

**20 mg / 10 ml**

**accord**

**1 vial**

Code: Guj/Drugs/1026

LOT

EXP

**Epirubicin Hydrochloride**  
**2 mg/ml solution for injection or infusion**

Epirubicin Hydrochloride  
For Intravenous or intravesical use  
Read the package leaflet before use.

**50 mg / 25 ml**

**accord**

**1 vial**

Code: Guj/Drugs/1026

LOT

EXP

**Epirubicin Hydrochloride 2 mg/ml**  
**solution for injection or infusion**

Epirubicin Hydrochloride  
For Intravenous or intravesicle use  
Read the package leaflet before use.

**200 mg/100 ml**

**accord**

**1 vial**

Code : Guj/Drugs/1026

Lot:

Exp:

## 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 hydrochloride 2 mg/mL Solution for Injection for the following indications:

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

- Carcinoma of the breast
- Gastric cancer

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.
- Prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection

Is approvable.

#### EXECUTIVE SUMMARY

##### Problem statement

This was an abridged, decentralised application for Epirubicin hydrochloride 2 mg/mL Solution for Injection, submitted under Article 10(1) (generic application) of Directive 2001/83/EC (as amended). The reference medicinal product authorised for not less than 10 years is Pharmorubicin 2 mg/mL Solution for Injection (Pharmacia Limited), PL 00032/0275, licensed in the UK on 14.05.2004). This application was submitted as a medically targeted abridged application to add a new indication for the treatment of breast cancer, with reference to the original UK product, Pharmorubicin 2 mg/mL Solution for Injection (PL 03433/0135), granted on 18/01/1991 (since cancelled). The RMS is the UK and the CMS are detailed in the cover page.

##### About the product

Epirubicin, the 4-epimer of doxorubicin, is an anthracycline glycoside antineoplastic antibiotic that is a semisynthetic derivative of daunorubicin. Its action is related to its ability to bind to DNA leading to the inhibition of nucleic acid synthesis and mitosis. Epirubicin is not orally absorbed. Following iv administration, epirubicin is rapidly and widely distributed into the tissues with the highest concentrations found in the liver, spleen, kidney, and the small intestines. Binding of epirubicin to plasma proteins, predominantly albumin is about 77% and is not affected by drug concentration. Epirubicin also appears to concentrate in red blood cells; whole blood concentrations are approximately twice those of plasma.

Epirubicin is metabolized mainly in the liver, but also in other tissues, into epirubicinol which is also active. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours. Biliary excretion is the major route of elimination, 40% of the administered dose being recovered in the bile in 72 hours. The drug does not cross the blood-brain-barrier.



When epirubicin is administered intravesically the systemic absorption is minimal. The benefits of anthracyclines (doxorubicin, daunorubicin, epirubicin and idarubicin) in the treatment of malignant disease are known for decades. However, a major limitation to the use of anthracyclines is cardiotoxicity.

**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 this product type at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, 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 those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites. In particular, a certificate of GMP is provided for the site of finished product manufacture. The certificate indicates that the site is suitable for the manufacture of sterile, aseptically-prepared oncology products.

Assurance has been provided that the active substance manufacturer operates in accordance with the principles of GMP from the QPs of the sites for batch release and finished product manufacture.

## **SCIENTIFIC OVERVIEW AND DISCUSSION**

### **Quality aspects**

#### **Drug substance**

The chemical-pharmaceutical documentation and Expert Report in relation to epirubicin hydrochloride are of sufficient quality in view of the present European regulatory requirements.

The quality of the drug substance is supported by a Ph.Eur. Certificate of Suitability (CEP). The control tests and specifications for drug substance product are adequately drawn up. A retest period of 2 years is stated on the CEP.

#### **Drug Product**

The development of the product has been described, the choice of excipients is justified and their functions explained. The manufacturing process is described adequately. Media fill trials to confirm the validity of the proposed manufacturing process and sterilisation method are presented.

The product specifications cover appropriate parameters for this dosage form. Validation reports for the analytical methods have been presented for all methods. Batch analysis data are presented for exhibit batches. The results show that the finished products meet the specifications proposed.

Stability trials on exhibit batches of the product, which are at least 10 % of proposed commercial batch size have been initiated, with data available. The proposed testing protocol is presented. The frequency of testing under all conditions is considered satisfactory. Testing is performed in line with the finished product shelf life specification. An adequate post-approval stability protocol and stability commitment is provided. The stability data are sufficient to support the proposed shelf life of 24 months at  $5 \pm 3$  °C. A bioequivalence study is not required as the product is a solution for injection or infusion.

### **Non clinical aspects**

The pharmacological, pharmacokinetic and toxicological properties of epirubicin Hydrochloride are well known. As epirubicin hydrochloride is a well known active substance, no further studies are required and the applicant has provided none. An overview based on a literature review is thus appropriate.

### **Clinical aspects**

#### **Pharmacokinetics and Pharmacodynamics**

As this is a submission for a generic product as a solution for infusion, no new pharmacokinetic and pharmacodynamic studies have been carried out.

#### **Clinical studies (efficacy and safety)**

No new no clinical studies have been performed and none are required for this application.

#### **Summary of Product Characteristics, Patient Information Leaflet and Labelling**

These were satisfactory.

The MAH has an appropriate system of Pharmacovigilance in place and a detailed description of the Pharmacovigilance system is included in the documentation.

### **BENEFIT RISK ASSESSMENT**

Epirubicin, when used as indicated, has a favourable benefit-to-risk profile. As shown in the various clinical settings patients have drawn benefit from therapy with Epirubicin as single substance or as part of a drug combination. The hazard associated with epirubicin appears to be low and acceptable when considered in relation to its therapeutic benefits. The formulation of Epirubicin Hydrochloride 2 mg/mL can be considered essentially similar to Pharmorubicin Solution for Injection 2mg/mL. The efficacy and safety profiles of the two products would therefore be expected to be equivalent. The therapeutic indications given in the applicant's product's SPC are in line with those approved for Pharmorubicin Solution for Injection 2mg/mL. Therefore the benefit-risk ratio for **Epirubicin Hydrochloride 2 mg/mL** could be considered similar to that of Pharmorubicin. A Marketing authorisation was therefore granted.

## **Module 6**

### **Steps taken after procedure**

No non-confidential changes have been made to the Marketing Authorisation.