SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin Hydrochloride 10 mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg of epirubicin hydrochloride
After reconstitution, each vial contains 2 mg/ml epirubicin hydrochloride
Excipient with known effect
Each 10 mg vial contains 2 mg of methyl hydroxybenzoate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection
A sterile freeze dried orange red coloured lyophilised cake.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epirubicin hydrochloride is used in the treatment of a range of neoplastic conditions, including:
• Carcinoma of the breast,
• Advanced ovarian cancer,
• Gastric cancer,
• Lung and colorectal carcinomas,
• Malignant lymphomas,
• Leukaemias
• Multiple myeloma.

When administered intravesically, epirubicin hydrochloride has been shown to be beneficial in the treatment of:
• Papillary transitional cell carcinoma of the bladder,
• Carcinoma-in-situ of the bladder
• Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection.

4.2 Posology and method of administration

Posology

Epirubicin hydrochloride is for intravenous or intravesical use only.

Preparation of the freeze-dried powder

The product should be dissolved in 5 ml 0.9% sodium chloride or water for injections to get the final concentration of 2 mg/ml. The vial contents will be under a negative pressure. To minimize aerosol formation during reconstitution, particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided. After gentle agitation the reconstituted solution will be transparent and red in appearance.

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.

Paediatric population

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

Dosage

In order to avoid cardiac toxicity, a total cumulative dose of 900 – 1,000 mg/m² epirubicin hydrochloride should not be exceeded (see section 4.4).

Conventional doses

When epirubicin hydrochloride is used as a single agent, the recommended dosage in adults is 60-90 mg/m² body surface area. Epirubicin hydrochloride should be injected intravenously over 3-5 minutes. The dose should be repeated at 21 days intervals, depending upon the patients' 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.

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

**Lung cancer**

— Small cell lung cancer (previously untreated): 120 mg/m\(^2\) epirubicin hydrochloride on day 1, every 3 weeks.

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

For high dose treatment, epirubicin hydrochloride may be given as an intravenous bolus over 3-5 minutes or as an infusion of up to 30 minutes duration.

**Breast cancer**

In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin hydrochloride ranging from 100 mg/m\(^2\) (as a single dose on day 1) to 120 mg/m\(^2\) (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\(^2\) for conventional treatment and 105-120 mg/ m\(^2\) for high dose schedules) 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 hydrochloride are commonly used in monotherapy and combination chemotherapy for various other tumours, as shown:

<table>
<thead>
<tr>
<th>Cancer indication</th>
<th>Epirubicin hydrochloride dose (mg/m(^2))^(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Advanced ovarian cancer</td>
<td>60 - 90</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>60 – 90</td>
</tr>
<tr>
<td>SCLC</td>
<td>120</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Intravesical administration of 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</td>
</tr>
<tr>
<td><strong>Combination therapy</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 - 100</td>
</tr>
<tr>
<td></td>
<td>120</td>
</tr>
</tbody>
</table>

^a Doses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals
If epirubicin hydrochloride is used in combination with other cytotoxic products, the doses should be reduced accordingly. Commonly used doses are shown in the table above.

**Hepatic impairment**

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

<table>
<thead>
<tr>
<th>Serum bilirubin</th>
<th>SGOT</th>
<th>Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4-3mg/100ml</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>&gt; 3mg/100ml</td>
<td>&gt; 4 times upper normal limit</td>
<td>75%</td>
</tr>
</tbody>
</table>

**Renal impairment**

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin hydrochloride excreted by this route. However, dosage adjustment may be necessary in patients with serum creatinine > 5 mg/dL.

**Intravesical administration:**

Epirubicin hydrochloride can be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be given intravesically for the treatment of invasive tumours that have penetrated the bladder wall, systemic therapy or surgery is more appropriate in these situations (see section 4.3). Epirubicin hydrochloride has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours in order to prevent recurrences.

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 water for injection).

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 INSTALLATION SOLUTIONS**

<table>
<thead>
<tr>
<th>Dose Epirubicin hydrochloride required</th>
<th>Volume of 2 mg/ml epirubicin hydrochloride injection</th>
<th>Volume of diluent sterile water for injection or 0.9% sterile saline</th>
<th>Total volume for bladder installation</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>15 ml</td>
<td>35 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>50 mg</td>
<td>25 ml</td>
<td>25 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>80 mg</td>
<td>40 ml</td>
<td>10 ml</td>
<td>50 ml</td>
</tr>
</tbody>
</table>
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 hydrochloride is contraindicated in:

- Patients who have demonstrated hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or to other anthracyclines or anthracenediones
- Lactation (see section 4.6)

For intravenous administration

- persistent myelosuppression
- previous treated with maximum cumulative doses of epirubicin hydrochloride and/or other anthracyclines and anthracenediones (see section 4.4)
- severe hepatic impairment
- severe myocardial insufficiency
- recent myocardial infraction
- severe arrhythmias
- patients with acute systemic infections
- unstable angina pectoris
- myocardiopathy
- acute inflammatory heart diseases

For intravesical administration, epirubicin hydrochloride is contraindicated in:

- urinary tract infections
- invasive tumours penetrating the bladder
- catheterisation problems
- large volume of residual urine
- contracted bladder
- inflammation of the bladder
- haematuria

4.4 Special warnings and precautions for use

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

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

While treatment with high doses of epirubicin hydrochloride (e.g. $\geq 90 \text{ mg/m}^2$ every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/m2 every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucositis may be increased. Treatment with high doses of epirubicin hydrochloride does require special attention for possible clinical complications due to profound myelosuppression.

**Reproductive system**

Epirubicin hydrochloride can have genotoxic effects.

Women should not become pregnant during treatment with epirubicin hydrochloride.

Men and women treated with epirubicin hydrochloride should adopt appropriate contraception. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available.

**Extravasation**

Extravasation of epirubicin hydrochloride during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein. Should signs or symptoms of extravasation occur during intravenous administration of epirubicin hydrochloride the infusion of the medicinal product should be immediately discontinued. The adverse effect of extravasation of anthracyclines may be prevented or reduced by immediate use of a specific treatment e.g. dextrazonxane (please refer to relevant labels for use). The patient's pain may be relieved by cooling down the area and keeping it cool, use of hyaluronic acid and DMSO. The patient should be monitored closely during the subsequent period of time, as necrosis may occur after several weeks. If extravasation occurs, a plastic surgeon should be consulted with a view to possible excision.

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

**Haematological toxicity**

As with other cytotoxic agents, epirubicin hydrochloride may produce myelosuppression. Haematologic profiles should be assessed before and during each cycle of therapy with epirubicin hydrochloride, including
differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin hydrochloride haematologic toxicity and is the most common acute dose-limiting toxicity of this medicinal product.

During treatment with epirubicin hydrochloride, 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 generally more severe with high-dose schedules, reaching the nadir in most cases between days 10 and 14, after administration of the medicinal product; this is usually transient with the WBC/neutrophil counts returning to normal values in most cases by day 21. Thrombocytopenia and anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicemia, septic shock, haemorrhage, tissues hypoxia, or death.

Secondary leukaemia

Secondary leukaemia, with or without a preleukaemic phase, has been reported in patients treated with anthracyclines, including epirubicin hydrochloride. Secondary leukaemia is more common when such medicinal products are given in combination with DNA-damaging antineoplastic agents, in combination with radiation treatment, when patients have been heavily pre-treated with cytotoxic medicinal products, or when doses of the anthracyclines have been escalated. These leukaemias can have a 1- to 3 year latency period (see section 5.1).

Gastrointestinal

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

Patients must have adequately recovered from acute toxicities (such severe stomatitis, mucositis, neutropenia, thrombocytopenia and generalized infections) of prior cytotoxic treatment before starting treatment with epirubicin hydrochloride.

Cardiac function

Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.

Early (i.e. acute) events

Early cardiotoxicity of epirubicin hydrochloride consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia, and bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These
effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally transient, reversible and not a consideration for the discontinuation of epirubicin hydrochloride treatment.

Late (i.e. delayed) events

Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin hydrochloride or within 2 to 3 months after treatment termination, but later events (several months to years after completion of treatment) have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the medicinal product.

The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin hydrochloride in excess of 900 mg/m²; this cumulative dose should only be exceeded with extreme caution (see section 5.1).

In establishing the maximal cumulative dose of epirubicin hydrochloride, consideration should be given to any concomitant therapy with potentially cardiotoxic drugs. A cumulative dose of 900-1000 mg/m² should only be exceeded with extreme caution with both conventional and high doses of epirubicin hydrochloride. 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/m², 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 hydrochloride should be discontinued.

Cardiomyopathy induced by anthracyclines is associated with a persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP) and a reduction of the ejection fraction (LVEF). Electrocardiogram (ECG) changes may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other medicinal products with the ability to suppress cardiac contractility or cardiotoxic medicinal products (e.g. trastuzumab) (see section 4.5) with an increased risk in the elderly.
Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with epirubicin hydrochloride may occur at lower cumulative doses whether or not cardiac risk factors are present.

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

**Cardiotoxicity in combination with trastuzumab**

Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving trastuzumab therapy alone or in combination with anthracyclines such as epirubicin hydrochloride. This may be moderate to severe and has been associated with death.

Trastuzumab and anthracyclines such as epirubicin hydrochloride should not be used currently in combination except in a well-controlled clinical trial setting with cardiac monitoring. Patients who have previously received anthracyclines are also at risk of cardiotoxicity with trastuzumab treatment, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.

Because the half-life of trastuzumab is approximately 28-38 days, trastuzumab may persist in the circulation for up to 27 weeks after stopping trastuzumab treatment. Patients who receive anthracyclines such as epirubicin hydrochloride after stopping trastuzumab may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab. If anthracyclines such as epirubicin hydrochloride are used, the patient's cardiac function should be monitored carefully.

If symptomatic cardiac failure develops during trastuzumab therapy after epirubicin hydrochloride therapy, it should be treated with the standard medications for this purpose.

**Monitoring of cardiac function**

Cardiac function should be assessed before patients undergo treatment with epirubicin hydrochloride and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment.

The risk may be decreased through regular monitoring of left ventricular ejection fraction (LVEF) during the course of treatment with prompt discontinuation of epirubicin hydrochloride at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased
cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m² epirubicin hydrochloride should be exceeded only with extreme caution.

Tumour-lysis syndrome

Epirubicin hydrochloride may induce hyperuricaemia because of the extensive purine catabolism as a result of rapid lysis of neoplastic cells (tumour-lysis syndrome) induced by the medicinal product. Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumour-lysis syndrome.

Other

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

Heart failure may appear even several weeks after discontinuing therapy with epirubicin hydrochloride 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).

Liver function

The major route of elimination of epirubicin hydrochloride is the hepatobiliary system. Before starting therapy with epirubicin hydrochloride, and if possible during treatment, liver function should be evaluated (serum total bilirubin, AST, SGOT, SGT, alkaline phosphatase, bilirubin) (see section 4.2). Patients with elevated bilirubin or AST may experience slower clearance of the medicinal product with an increase in overall toxicity. Lower doses are recommended in these patients (see sections 4.2 and 5.2). Patients with severe hepatic impairment should not receive epirubicin hydrochloride (see section 4.3).

Renal function

Serum creatinine should be assessed before and during therapy. Dosage adjustment is necessary in patients with serum creatinine > 5 mg/dl (see section 4.2).

Effects at site of injection
Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see section 4.2).

**Immunosuppressant effects/Increased susceptibility to infections**

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including epirubicin hydrochloride, may result in serious or fatal infections (see section 4.5). Killed or inactivated vaccines may be administered to patients receiving epirubicin hydrochloride; however, the response to such vaccines may be diminished.

Epirubicin hydrochloride may impart a red colour to the urine for 1-2 days after administration.

**Additional warnings and precautions for other routes of administration**

*Intravesical route*

Administration of epirubicin hydrochloride may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, haematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterization problems (e.g., uretheral obstruction due to massive intravesical tumours).

*Intra-arterial route*

Intra-arterial administration of epirubicin hydrochloride (transcatheter arterial embolization for the localized or regional therapies of primary hepatocellular carcinoma or liver metastases) may produce (in addition to systemic toxicity qualitatively similar to that observed following intravenous administration of epirubicin hydrochloride) localized or regional events which include gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to drug induced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue.

**Excipients**

Epirubicin hydrochloride, powder for solution for injection, contains methyl hydroxybenzoate. This may cause allergic reactions (which may occur after treatment), and in are cases, respiratory difficulties.

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

Dexverapamil may alter the pharmacokinetics of epirubicin hydrochloride and possibly increase its bone marrow depressant effects.
Prior administration of higher doses (900 mg/m² and 1200 mg/m²) of dexrazoxane may increase the systemic clearance of epirubicin hydrochloride and result in a decrease in AUC.

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

The co-administration of interferon \( \alpha_{2b} \) may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin hydrochloride.

Anthracyclines including epirubicin hydrochloride should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The half-life of trastuzumab is approximately 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

When given prior to epirubicin hydrochloride, paclitaxel may affect the pharmacokinetics (increased plasma concentrations) of epirubicin hydrochloride and its metabolite, epirubicinol the latter being, however, neither toxic nor active. Co-administration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin hydrochloride when epirubicin hydrochloride was administered prior to the taxane. This combination may be used if using staggered administration between the two agents. Infusion of epirubicin hydrochloride and paclitaxel should be performed with at least a 24 hour interval between the 2 agents.

In one study, haematological toxicity was greater when paclitaxel was administered before epirubicin hydrochloride compared with after epirubicin hydrochloride. One study has shown that paclitaxel clearance is reduced by epirubicin hydrochloride.

Quinine may accelerate the initial distribution of epirubicin hydrochloride from blood into the tissues and may have an influence on the red blood cells partitioning of epirubicin hydrochloride.

Cimetidine 400 mg b.i.d given prior to epirubicin hydrochloride 100 mg/m² every 3 weeks led to a 50% increase in epirubicin hydrochloride AUC and a 41% increase in epirubicinol AUC (latter <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. Therefore, it should be discontinued during treatment with epirubicin hydrochloride.

Epirubicin hydrochloride is mainly used in combination with other cytotoxic medicinal products. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastro-intestinal effects (see section 4.4)

The possibility of a marked disturbance of haematopoiesis needs to be kept in mind when patients have been previously treated with medication which affects the bone marrow (i.e. cytostatic agents, sulphonamide, chloramphenicol, diphenylhydantoin, amidopyrine-derivatives, antiretroviral agents).
Increase of myelosuppression may occur in patients receiving combination therapy of anthracycline and dexrazoxane.

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.

The use of epirubicin hydrochloride in combination chemotherapy with other potentially cardiotoxic medicinal products, as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), requires monitoring of cardiac functions throughout treatment.

Epirubicin hydrochloride is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicin hydrochloride metabolism, pharmacokinetics, therapeutic efficacy and/ or toxicity (see section 4.4).

This product is generally not recommended in combination with live attenuated vaccines. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

4.6 Pregnancy and lactation
See also section 5.3.

Like most other anti-cancer agents, epirubicin hydrochloride has shown mutagenic and carcinogenic properties in animals. Both men and women receiving epirubicin hydrochloride should be informed of the potential risk of adverse effects on reproduction and should use an effective method of contraception during treatment.

Fertility

Epirubicin hydrochloride could induce chromosomal damage in human spermatozoa. Male patients treated with epirubicin hydrochloride are advised not to father a child during treatment and to seek advice on conservation of sperm prior to treatment because of the possibility of infertility due to therapy with epirubicin hydrochloride.

Epirubicin hydrochloride may cause amenorrhea or premature menopause in premenopausal women.

Pregnancy

Experimental data in animals suggest that epirubicin hydrochloride may cause foetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant during treatment. And they 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 hydrochloride therapy. In cancer chemotherapy,
epirubicin hydrochloride 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. There are no studies in pregnant women.

**Breast-feeding**

This product should not normally be administered to patients who are pregnant or to mothers who are breast-feeding.

Epirubicin hydrochloride has been shown to be excreted into the milk of rats. It is not known whether epirubicin hydrochloride is excreted into human breast milk. Because many medicinal products, including other anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from epirubicin hydrochloride, mothers should discontinue nursing prior to taking this medicinal product.

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

There have been no reports of particular adverse events relating to effects on ability to drive and to use machines and it has not been systematically evaluated.

Epirubicin hydrochloride 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

The following undesirable effects have been observed and reported during treatment with epirubicin hydrochloride with the following frequencies: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated form the available data).

More than 10 % of treated patients can expect to develop undesirable effects. The most common undesirable effects are myelosuppression, gastrointestinal side effects, anorexia, alopecia, infection.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Very common</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Septic shock, sepsis, pneumonia</td>
</tr>
<tr>
<td>Condition Type</td>
<td>Frequency</td>
<td>Description</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</td>
<td>Uncommon</td>
<td>Acute lymphocytic leukaemia, acute myelogenous leukaemia (see section 4.4)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common</td>
<td>Myelosuppression (leukopenia, granulocytopenia and neutropenia, anaemia and febrile neutropenia, thrombocytopenia)</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Haemorrhage and tissue hypoxia as result of myelosuppression</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Anaphylaxis (anaphylactic/anaphylactoid reactions with or without shock including skin rash, pruritus, fever and chills), allergic reactions following intravesical administration</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Very common</td>
<td>Loss of appetite</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Hyperuricemia (see section 4.4)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Rare</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>Conjunctivitis, keratitis</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common</td>
<td>Congestive heart failure (CHF) (dyspnoea, oedema, hepatomegaly, ascites, pulmonary oedema, pleural effusions, extrasystoles)</td>
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<tr>
<td></td>
<td>Rare</td>
<td>Cardiotoxicity (e.g. ECG abnormalities, arrhythmias, cardiomyopathy), ventricular tachycardia, bradycardia, AV block, bundle-branch block (see section 4.4)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Hot flashes</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Phlebitis, thrombophlebitis</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Shock</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Thromboembolism, including pulmonary emboli</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Mucositis, stomatitis, vomiting, diarrhoea, nausea, which can result in loss of appetite and abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Oral pain, mucosal burning sensation, oesophagitis</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Gastric erosion and ulcers, gastrointestinal haemorrhage, hyperpigmentation of the oral mucous membranes</td>
</tr>
<tr>
<td>Disorders</td>
<td>Not known</td>
<td>Oral mucosa erosion, mouth haemorrhage</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Very common</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Common</td>
<td>Local skin and tissue toxicity, rash, pruritus</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Skin changes, erythema, flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction)</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>Urticaria</td>
<td></td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td>Very common</td>
<td>Red colouration of urine for 1 to 2 days after administration</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td>Common</td>
<td>Amenorrhoea</td>
</tr>
<tr>
<td>Rare</td>
<td>Azoospermia</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Common</td>
<td>Infusion site erythema. Paravenous injection can cause tissue necrosis. Malaise, asthenia, fever</td>
</tr>
<tr>
<td>Rare</td>
<td>Chills</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Not known</td>
<td>Phlebosclerosis, local pain, severe cellulitis</td>
</tr>
<tr>
<td>Common</td>
<td>Changes in transaminase levels, Asymptomatic decreases in left ventricular ejection fraction (LVEF)</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration (see section 4.4)</td>
<td></td>
</tr>
</tbody>
</table>

**Blood and lymphatic system disorders**

High doses of epirubicin hydrochloride have been safely administered in a large number of untreated patients having various solid tumours and have caused adverse events which are not different from those seen at conventional doses with the exception of reversible severe neutropenia (< 500 neutrophils/mm³ 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.

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

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

**Skin and subcutaneous tissue disorders**

Alopecia, normally reversible, appears in 60 – 90 % of treated cases; it is accompanied by lack of beard growth in males.

**General disorders and administration site conditions**

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.

Local pain and tissue necrosis (following accidental paravenous injection) may occur.

**Intravesical administration**

As only a small amount of active ingredient is reabsorbed after intravesical instillation, severe systemic adverse reactions as well as allergic reactions are rare. Commonly reported are local reactions like burning sensation and frequent voiding (pollakisuria). Occasional bacterial or chemical cystitis have been reported (see section 4.4). These ADRs are mostly reversible.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via www.mhra.gov.uk/yellowcard.

**4.9 Overdose**

**Symptoms**

Very high single doses of epirubicin hydrochloride may be expected to cause acute myocardial degeneration mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications 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 antibiotics, blood transfusion and reverse barrier nursing. Latent cardiac failure has been observed with anthracyclines several months to years after completion of treatment (see section 4.4). 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 guidelines.

**Treatment**
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent ATC code: L01DB03

Epirubicin hydrochloride is a cytotoxic active antibiotic from the anthracycline group. The mechanism of action of epirubicin hydrochloride 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 hydrochloride 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/m² of the medicinal product 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/m² there is an extensive linear pharmacokinetic, 150 mg/m² 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 hydrochloride 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 hydrochloride from doxorubicin and may account for the faster elimination of epirubicin hydrochloride 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 active substance.

Epirubicin hydrochloride 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 active substance does not cross the blood-brain-barrier.

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

Epirubicin hydrochloride, like other anthracyclines, was mutagenetic, genotoxic, and carcinogenic in rats. Embryotoxicity was seen in rats at clinically relevant doses.

No malformations were seen in rats or rabbits, but like other anthracyclines and cytotoxic active substances, epirubicin hydrochloride must be considered potentially teratogenic.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Methyl hydroxybenzoate (E218),
Lactose monohydrate,
Hydrochloric acid,
Water for injection.
6.2 Incompatibilities
Prolonged contact of the medicinal product with any solution of an 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 6.3 should be used.

A physical incompatibility of the medicinal product with heparin has been reported.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
Shelf life of the product as packaged for sale: 2 years
Shelf life after reconstitution according to directions:

In-use stability has been demonstrated for 24 hours at 15°C - 25°C and for 48 hours at 2 - 8°C in water for injections and 0.9% w/v sodium chloride solution. However from a microbiological point of view, it is recommended that the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage
Store below 30°C.

Keep the vial in the outer carton.

For storage conditions of the reconstituted medicinal product, see section 6.3
6.5 **Nature and contents of container**

Epirubicin hydrochloride 10 mg is produced in 10 ml Type I moulded flint glass vial with 20 mm bromo butyl rubber stoppers and 20 mm aluminium flip-off tear-off seal.

1 vial per pack

6.6 **Special precautions for disposal**

Epirubicin hydrochloride may be further diluted in glucose 5% solution or sodium chloride 0.9% solution and administered as an intravenous infusion. For information on the stability of the infusion solutions please refer to section 6.3.

The injection solution contains no preservative and any unused portion of the vial should be disposed of 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**

Cipla (EU) Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
8  MARKETING AUTHORISATION NUMBER(S)
   PL 36390/0108

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY
   14/04/2011

10 DATE OF REVISION OF THE TEXT
    11/05/2017