Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin 2 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of solution for injection contains 2 mg epirubicin hydrochloride.
The content of sodium is 3.54mg per ml and per vial is as follows:
5ml vial 17.71mg, 10ml vial 35.42mg, 25ml vial 88.55mg, 50ml vial 177.1mg and 100ml vial 354.2mg
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for Injection.

A clear red solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- - Carcinoma of the breast
- - Advanced ovarian cancer
- - Gastric cancer
- - Small cell lung 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
Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection

4.2 Posology and method of administration

Epirubicin is for intravenous or intravesical use only.
The safety and efficacy of epirubicin in children has not been established.
Epirubicin 2 mg/ml Solution for Injection is compatible with both dextrose 5% and sodium chloride 0.9%.
Please refer to section 6.6 for instructions on the preparation and handling of the drug product.
Intravenous administration
It is advisable to administer epirubicin via the tubing of a free-running intravenous sodium chloride 0.9% 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^2 body area. Epirubicin should be injected intravenously over 3-5 minutes. The dose should be repeated at 21-day intervals, depending upon the patient's haematological status and bone marrow function.
If signs of toxicity, including severe neutropenia/neutropenic fever and thrombocytopenia occur (which could persist at day 21), dose modification or postponement of the subsequent dose may be required.
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^2 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^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 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:

	Epirubicin Dose (mg/m ^{2}) [a]	
Cancer Indication	**Monotherapy**	**Combination Therapy**
Advanced 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	

[a] 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.

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 Dose Reduction
24 - 51 µmol/l 50%

> 51 µmol/l 75%

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

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

For the treatment of superficial bladder cancer the following regimen is recommended, using the dilution table below:
8 weekly instillations of 50 mg/50 ml (diluted with sodium chloride 0.9%).
If local toxicity is observed: A dose reduction to 30 mg/50 ml is advised.
Carcinoma in situ of the bladder: Up to 80 mg/50 ml (depending on individual tolerability of the patient).
For prophylaxis: 4 weekly administrations of 50 mg/50 ml followed by 11 monthly instillations at the same dose.

DILUTION TABLE FOR BLADDER INSTILLATION SOLUTIONS

Dose Epirubicin required	Volume of 2 mg/ml epirubicin injection	Volume of diluent sterile sodium chloride 0.9%	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 hours. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. During the instillation, the patient should be rotated occasionally and should be instructed to void urine at the end of the instillation time.

4.3 Contraindications

Epirubicin is constraindicated in:

- - Patients who have demonstrated hypersensitivity to epirubicin, other anthracyclines or anthracenediones or to any of the excipients.
- - Lactation

Intravenous use

- - Myocardiopathy
- - Persistent myelosuppression
- - Patients with marked myelosuppression induced by previous treatment with either other anti-neoplastic agents or radiotherapy.
- - Patients treated with maximal cumulative doses of Epirubicin or other anthracyclines such as doxorubicin or daunorubicin or anthracenediones (see section 4.4.).
- - Patients with current or previous history of cardiac impairment (including New York Heart Association (NYHA) class IV heart failure, acute myocardial infarction and previous infarction with residual NYHA class III or class IV heart failure, acute inflammatory heart diseases, arrhythmia with serious haemodynamic consequences).
- - Patients with acute systemic infections
- - Unstable angina pectoris
- - Severe liver impairment
- - Severe mucositis of the mouth, pharynx, oesophagus, and gastro-intestinal tract.

For intravesical administration, epirubicin is contraindicated in:
- Urinary tract infections
- Invasive tumours penetrating the bladder
- Catheterisation problems
- Vesical inflammation
- Large volume of residual urine
- Hematuria
- Contracted bladder.

4.4 Special warnings and precautions for use

General
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.

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

While treatment with high doses of epirubicin (e.g., ≥ 90 mg/ m^2 every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/ m^2 every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucositis may

be increased. Treatment with high doses of epirubicin does require special attention for possible clinical complications due to profound myelosuppression.

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

Early (i.e. Acute) Events. Early cardiotoxicity of epirubicin consist 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 not a consideration for the discontinuation of epirubicin treatment.

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

The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin in excess of 900 mg/ m^2; this cumulative dose should only be exceeded with extreme caution (see section 5.1).

Cardiomyopathy induced by anthracyclines is associated with persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the ejection fraction. Cardiac monitoring of patients receiving epirubicin treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques. Electrocardiogram (ECG) changes may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity. The risk of serious cardiac impairment may be decreased through regular monitoring of left ventricular ejection fraction (LVEF) during the course of treatment with prompt discontinuation of epirubicin at the first sign of impaired function. The preferred method for repeated assessment of cardiac function is evaluation of LVEF measure by multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increase cardiac toxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through follow-up. In patients with risk factors, particularly prior anthracycline or anthracenedione use, the monitoring of cardiac function must be particularly strict.

Given the risk of cardiomyopathy, a cumulative dose of 900 mg/ m^2 epirubicin should be exceeded only with extreme caution.

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 with active or dormant cardiovascular disease, who have received concomitant, or prior, radiotherapy to the mediastinal pericardial area, previous therapy with other anthracyclines or anthracenediones and/or who are under medical treatment with potentially cardiotoxic medicinal products (e.g. trastuzumab) (see section 4.5). The risk of cardiotoxicity is also increased in the elderly.

Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving trastuzamab therapy alone or in combination with anthracyclines such as epirubicin. This may be moderate to severe and has been associated with death.
Trastuzumab and anthracyclines such as epirubicin 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 traztuzumab and anthracyclines. Because the half-life of trastuzumab is approximately 4-5 weeks, trastuzumab may persist in the circulation for up to 20-25 weeks after stopping trastuzumab treatment. Patients who receive anthracyclines such as epirubicin after stopping trastuzumab may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy for up to 25 weeks after stopping trastuzumab. If anthracyclines such as epirubicin are used, the patient's cardiac function should be monitored carefully.
If symptomatic cardiac failure develops during trastuzumab therapy after epirubicin therapy, it should be treated with the standard medications for this purpose. Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with epirubicin may occur at lower cumulative doses

whether or not cardiac risk factors are present. It is probable that the toxicity of epirubicin and other anthracyclines or anthracenediones is additive

Hematologic Toxicity
As with other cytotoxic agents, epirubicin may produce myelosuppression. 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.

Hematologic profiles should be assessed before and during each cycle of therapy with epirubicin,including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopenia and neutropenia are usually transient with conventional and high-dose schedules reaching a nadir between the 10^{th} and 14^{th} day, values should return to normal by the 21^{st} day; they are more severe with high dose schedules.

Thrombocytopenia (< 100,000 platelets/mm^3) is experienced in very few patients, even following high doses of epirubicin. Anaemia may also occur.

Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.

Secondary Leukemia
Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines, including epirubicin. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, in combination with radiation treatment, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukemias can have a 1- to 3-year latency period.

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

Liver Function
The major route of elimination of epirubicin is the hepatobiliary system. Before commencing therapy with epirubicin, and during treatment, liver function should be evaluated (SGOT, SGT, AST, alkaline phosphatase, bilirubin), (see section 4.2). Patients with elevated bilirubin or AST may experience slower clearance of drug 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 (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).

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

Should signs or symptoms of extravasation occur during intravenous administration of epirubicin, the drug infusion should be immediately discontinued. The adverse effect of extravasation of anthracyclines may be prevented or reduced by immediate use of a specific treatment e.g. dexrazoxane (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 extravasation occurs, a plastic surgeon should be consulted with a view to possible excision.

Other

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

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

Immunosuppressant Effects/Increased Susceptibility to Infections
Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents including epirubicin, may result in serious or fatal infections (see section 4.5). Vaccination with a live vaccine should be avoided in patients receiving epirubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Reproductive system
Epirubicin can cause genotoxicity. Men and women should use an effective method of contraception during treatment and for six months thereafter (see section 4.6). Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available.

Additional warnings and precautions for other routes of administration

Intravesical route
Administration of epirubicin may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, hematuria, 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 tumors).

Intra-arterial route
Intra-arterial administration of epirubicin (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) 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.

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 interactions

It is not recommended that Epirubicin 2 mg/ml Solution for Injection be mixed with other medicinal products. However, epirubicin can be used in combination with other anti-cancer agents but patients should be monitored for additive toxicity, especially myelotoxicity and gastrointestinal toxicity.

If epirubicin is used concomitantly with other potentially cardiotoxic drugs, as well as other drugs that may cause heart failure, e.g. calcium channel blockers, then cardiac function must be monitored throughout the course of treatment (see section 4.4).

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.

Epirubicin is extensively metabolised in the liver; each concomitant medication which affects hepatic function can also affect the metabolisation or the pharmacokinetics of epirubicin and, consequently, its efficacy and/or toxicity (see section 4.4).

Anthracyclines including epirubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The half-life of trastuzumab is approximately 28.5 days and may persist in the circulation for up to 24 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 24 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Vaccination with a live vaccine should be avoided in patients receiving epirubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Drug interactions with epirubicin have been observed with cimetidine, dexverapamil, dexrazoxane, docetaxel, interferon α_2b, paclitaxel and quinine.

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

Prior administration of higher doses (900 mg/m^2 and 1200 mg/m^2) of dexrazoxane may increase the systemic clearance of epirubicin and result in a decrease in AUC. Increase of myelosuppression may occur in patients receiving combination therapy of anthracycline and dexrazoxane.

The co-administration of interferon α_2b may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin.

When given prior to Epirubicin, Paclitaxel may affect the pharmacokinetics (increase plasma concentrations) of epirubicin and its metabolite, epirubicinol (which is neither toxic nor active). 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.

Coadministration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when epirubicin was administered prior to the taxane. This combination may be used if using staggered administration between the two agents. Infusion of epirubicin and paclitaxel should be performed with at least a 24 hour interval between the 2 agents.

One study found that docetaxel may increase the plasma concentrations of epirubicin metabolites when administered immediately after 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^2 every 3 weeks led to a 50% increase in epirubicin AUC and a 41% increase in epirubicinol AUC (latter $p<0.05$). The AUC of the 7-deoxy-doxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P-450 activity. Cimetidine treatment should be discontinued during treatment with Epirubicin.

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

4.6 Fertility, pregnancy and lactation

Impairment of fertility

Epirubicin could induce chromosomal damage in human spermatozoa. Male patients treated with epirubicin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because of the possibility of infertility due to therapy with epirubicin.

Epirubicin may cause amenorrhea or premature menopause in premenopausal women.

Pregnancy

Women of childbearing potential should be advised to avoid becoming pregnant during treatment and fully informed of the potential hazard to the foetus.The possibility of genetic counselling should be considered if they become pregnant during epirubicin therapy.

Like most other anti-cancer agents, epirubicin has shown mutagenic and carcinogenic properties in animals.

If epirubicin is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. There are no studies in pregnant women

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

Both men and women receiving epirubicin should be informed of the potential risk of adverse effects on reproduction and should use an effective method of contraception during treatment and for six month thereafter.

Lactation
It is unknown whether epirubicin is excreted in human breast milk. Because many drugs, including other anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from epirubicin, breastfeeding must be discontinued before and during therapy with Epirubicin.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

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

System Organ Class	**Frequency**	**Undesirable effects**
Infections and infestations	Common	Infection
	Not Known	Septic shock, sepsis, pneumonia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rare	Acute lymphocytic leukemia, acute myelogenous leukemia
Blood and the lymphatic system disorders	Very Common	Thrombocytopenia, myelosuppression (leukopenia, granulocytopenia and neutropenia, anemia and febrile neutropenia), haemorrhage and tissue hypoxia as a result of myelosuppression.
Immune system disorders	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common	Anorexia, dehydration
	Rare	Hyperuricemia (see section 4.4)
Nervous system disorders	Rare	Dizziness
Eye disorders	Not known	Conjunctivitis,

System Organ Class	Frequency	Undesirable effects
		keratitis
Cardiac disorders	Rare	Congestive heart failure, (dyspnoea; oedema, hepatomegaly, ascites, pulmonary oedema, pleural effusions, gallop rhythm) cardiotoxicity (e.g. ECG abnormalities, arythmias, cardiomyopathy), ventricular tachycardia, bradycardia, AV block, bundle-branch block.
Vascular disorders	Common	Hot flashes, phlebitis
	Uncommon	Thrombophlebitis
	Not known	Shock, thromboembolism, including pulmonary emboli
Gastrointestinal disorders	Common	Loss of appetite, abdominal pain, oral mucosa erosion, mouth ulceration, oral pain, mucositis, esophagitis, stomatitis, vomiting, diarrhea, nausea, mouth haemorrhage, and buccal pigmentation
	Not Known	mucosal burning sensation,
Skin and subcutaneous tissue disorders	Very Common	Alopecia
	Common	Local toxicity, flushes
	Uncommon	Skin changes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction)
	Rare	Urticaria, rash, itch
	Not Known	Erythema
Renal and urinary disorders	Very common	Red coloration of urine for 1 to 2 days after

System Organ Class	Frequency	Undesirable effects
		administration
Reproductive system and breast disorders	Rare	Amenorrhea, azoospermia
General disorders and administration site conditions	Common	Infusion site erythema, phlebosclerosis, local pain, tissue necrosis after accidental paravenous injection
	Uncommon	Headache
	Rare	Malaise,/asthenia, fever, chills
	Not known	Severe cellulitis,
Investigations	Rare	Changes in transaminase levels
	Not Known	Asymptomatic drops in left ventricular ejection fraction
Injury, poisoning and procedural complications	Common	Chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration (see section 4.4).

Intravesical administration:
As only a small amount of active ingredient is reabsorbed after intravesical instillation, severe systemic adverse drug reactions as well as allergic reactions are rare. Commonly reported are local reactions like burning sensation and frequent voiding (pollakisuria).Occasional bacterial or chemical cystitis have been reported (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 IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Very high single doses of epirubicin will cause acute myocardial degeneration or complications within 24 hours and severe myelosuppression (mainly leukopenia and thrombocytopenia) within 10-14 days. Gastrointestinal toxic effects (mainly mucositis) will also occur. Latent cardiac failure has been observed with anthracyclines several months to years after completion of treatment (see section 4.4). Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines.

Treatment should be symptomatic and aim to support the patient during this period and should utilise such measures as antibiotics, blood transfusion and reverse barrier nursing. Epirubicin is not dialyzable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent. ATC code: L01D B03
Epirubicin is a cytotoxic active antibiotic from the anthracycline group.
The mechanism of action of epirubicin is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin has proved to be active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcomas SA 180 (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 and hepatic and renal function, plasma levels after intravenous injection of 60-150 mg/m^2 of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. Between 60 and 120 mg/m^2 there is an extensive linear pharmacokinetic, 150 mg/m^2 is at the margin of dose linearity. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.

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

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

Epirubicin is eliminated mainly through the liver, high plasma clearance values (0.91/min) indicate that this slow elimination is due to extensive tissue distribution. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours.

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

5.3 Preclinical safety data

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

Epirubicin, like other anthracyclines, was mutagenic, genotoxic, embryotoxic and carcinogenic in rats.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Water for Injections
Hydrochloric acid for pH adjustment

6.2 Incompatibilities

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

6.3 Shelf life

Shelf life before opening 2 years.

After first penetration of the stopper the Epirubicin Hydrochloride 2 mg/ml solution may be stored up to 24 hours at 2 to 8 ºC in the absence of light.
From a microbiological point of view, the product should be used immediately after first penetration of the rubber stopper and/or dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be more than 24 hours at 2 to 8 ºC, unless penetration/dilution has taken place in controlled and validated aseptic conditions.
From a chemical and physical point of view, the product should be used immediately after dilution. Any unused portion must be discarded after use.

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC).
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Epirubicin 2 mg/ml solution for injections is supplied in clear, type I borosilicate glass vials, for parenteral use, with chlorobutyl faced stoppers and aluminium seals with flip-off, containing 5ml, 10ml, 25ml, 50ml or 100ml of sterile solution of Epirubicin hydrochloride 2mg/ml.
Pack sizes:
Glass vials containing 5ml, 10ml, 25ml, 50ml and 100ml supplied in the following pack sizes:
1 x 5 ml, 1 x 10ml, 1 x 25 ml, 1 x 50 ml, 1 x 100 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The injection solution contains no preservative and any unused portion of the vial should be discarded immediately.

Epirubicin 2 mg/ml Solution for Injection is compatible with dextrose 5% and sodium chloride 0.9%.
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, irrigate with large amounts of water and/or 0.9% sodium chloride solution. Then seek medical evaluation by a physician.
5. In case of skin contact, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Always wash hands after removing gloves.
6. Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All cleaning materials should be disposed of as detailed below.
7. Pregnant staff should not handle the cytotoxic preparation.
8. Adequate care and precautions should be taken in the disposal of items (syringes, needles etc) used to reconstitute and/or dilute cytotoxic medicinal products. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd April 2009
Common renewal date: 11th December 2013

10 DATE OF REVISION OF THE TEXT

May 2019