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 5/10/25/50/100 ml vial contains 10/20/50/100/200 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
- Advanced Ovarian carcinoma
- 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.
- Prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection

4.2 Posology and method of administration

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

Conventional dose
Dosage regimen for conventional doses
When epirubicin is used as a single antiblastic agent, the recommended dose for adults is 60-90 mg/m^2 of body surface area to be administered via intravenous injection over 5 to 10 minutes at 21-day intervals, depending on the blood and bone marrow conditions.

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
Dosage regimen for high doses

Lung cancer

Epirubicin as a single agent in the treatment of lung cancer with high doses must be used according to the following schemes:

- Small cell lung cancer (SCLC) in non-pretreated patients: 120 mg/m^2 on day 1, every three weeks.

The drug must be administered as an intravenous bolus over 5-10 minutes or as an intravenous infusion over a maximum of 30 minutes.

Breast Cancer

In the adjuvant treatment of initial breast cancer with positive lymph nodes, the recommended doses vary from 100 mg/m^2 to 120 mg/m^2 administered every 3-4 weeks.

Lower doses (60-75 mg/m^2 or 105-120 mg/m^2 in high dosage regimens) are recommended for patients with reduced bone marrow reserves due to previous chemo-and/or radiotherapy treatments, elderly age, or with bone marrow neoplastic. The total dose per cycle can be divided over 2-3 consecutive 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
Ovarian cancer	60–90	50–100[b]
Gastric cancer	60–90	50
Small cell lung cancer (SCLC)	120	120[b]
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 11months	
Breast cancer		100-120[c]

a Doses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals.
b If used in combination with other anticancer drugs, the doses should be appropriately reduced.
c Lower doses (60-75 mg/m2 or 105-120 mg/m2 in high dosage regimens) are recommended for patients with reduced bone marrow function.

Bladder Cancer

Epirubicin can be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be used in this way for the treatment of invasive tumours which have penetrated the bladder wall where systemic therapy or surgery is more appropriate. Epirubicin has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours in order to prevent recurrences.

In the treatment of non-invasive transitional cell papillary carcinoma intravesical instillations of 50 mg (in 25-50 mL saline solution or distilled sterile water) are recommended once a week for eight weeks; in case of local toxicity (chemical cystitis), the unit dose must be reduced to 30 mg.
In the treatment of in-situ carcinoma, the dose may be increased to 80 mg depending on individual tolerability.

In the prophylaxis of relapses after transurethral resection of superficial tumors, intravesical instillations of 50 mg once a week for four weeks are recommended, followed by monthly instillations at the same dose for eleven months.

Impaired liver function

Most important elimination pathway of the drug is the hepatobiliary system, a dose reduction of Epirubicin is suggested for patients who have impaired liver function, in order to avoid global toxicity.

Generally speaking, when blood bilirubin levels are between 1.4-3 mg/100 Ml and bromosulfophthalein (BSF) retention is 9-15%, half the normal drug dose is recommended.

Serum Bilirubin	AST*	Dose Reduction
1.4 – 3 mg/100 ml		50%
> 3 mg/100 ml	> 4 times upper normal limit	75%

*AST – aspartate aminotransfera*se*

If bilirubin levels and BSF retention are higher still, a quarter of the normal dose is recommended.

Impaired renal function
Moderate impairment of renal function does not seem 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).

Method of administration
Epirubicin is for intravenous or intravesical use only.

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.
It is advisable to perform intravenous administration over 5-10 minutes. This technique reduces the risk of extravasation of the drug and ensures flushing of the vein at the end of administration.
In case of extravasation of Epirubicin during administration, there is a risk of tissue lesions, including necrosis.

Venous sclerosis may occur when the injection is administered into small vessels or is repeated in the same vein.

Intravesical administration
Epirubicin for instillation via a catheter must be kept in situ for an hour. The patient should be instructed not to drink any fluid in the 12 hours prior instillation. During instillation, it may be advisable to rotate the patient's pelvis to ensure broader contact of the solution with the bladder mucosa.

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 instillation
30 mg	15 ml	35 ml	50 ml
50 mg	25 ml	25 ml	50 ml
80 mg	40 ml	10 ml	50 ml

4.3 Contraindications

Epirubicin is contraindicated in:

- Patients who have demonstrated hypersensitivity to the active substance or to any of the excipients listed in section 6.1, other anthracyclines or anthracenediones.
- Breast-feeding

Intravenous use:

- Patients with persistent myelosuppression
- severe hepatic impairment
- severe myocardial insufficiency
- recent myocardial infarction
- severe arrhythmias
- previous treatments with maximum cumulative doses of epirubicin and/or other anthracyclines and anthracenediones (see section 4.4)
- patients with acute systemic infections

- unstable angina pectoris
- cardiomyopathy

Intravesical use:

- Urinary tract infections.
- Invasive bladder tumours.
- Catheterisation problems.
- Inflammation of the bladder.
- Haematuria

4.4 Special warnings and precautions for use

General
Epirubicin hydrochloride must be administered under the supervision of doctors who are experts in the use of cytotoxic therapies.
Before starting treatment with epirubicin hydrochloride, patients must recover from the acute toxicity of the previous cytotoxic therapy (such as stomatitis, neutropenia, thrombocytopenia, and generalised infections).

While treatment with high doses of epirubicin hydrochloride (e.g., ≥ 90 mg/m2 every 3 or 4 weeks) causes undesirable effects that are generally similar to those observed with standard doses (< 90 mg/m2 every 3 or 4 weeks), neutropenia and stomatitis/mucositis may be more severe. Treatment with high doses of epirubicin hydrochloride requires particular care because of the possible complications due to severe myelosuppression.

Cardiac Function - Cardiotoxicity is a risk of treatment with anthracyclines, which can manifest with acute or delayed events.

Acute toxicity. Early cardiotoxicity of epirubicin hydrochloride consists mainly of sinus tachycardia and/or 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.

Delayed toxicity. 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 or 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 dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.
The risk of developing congestive heart failure increases rapidly with the increase of total cumulative doses of over 900 mg/ m^2 of epirubicin hydrochloride; this cumulative dose must be exceeded only with extreme caution (see section 5.1).

Cardiac function must be evaluated prior to starting treatment with epirubicin hydrochloride and cardiac monitoring of patients receiving epirubicin treatment is highly important to minimise the risk of serious cardiac damage. 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 increased 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.

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

The risk factors for cardiac toxicity include active or silent cardiovascular disease, previous radiation therapy or concomitant radiation therapy on the pericardial mediastinal area, previous treatment with other anthracyclines or anthracenediones, concomitant use of medicinal products that suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab) (see section 4.5). The risk of cardiotoxicity is also increased in the elderly.

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

Trastuzumab and anthracyclines such as epirubicin must not usually be used in combination, except in well-controlled clinical studies 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.
It has been reported that trastuzumab has a variable half-life. Trastuzumab can remain in the circulation for up to seven months after interruption of treatment. Patients who receive anthracyclines, such as epirubicin, can be at increased risk of cardiotoxicity after interruption of treatment with trastuzumab. Whenever possible, the doctor must avoid anthracycline-based therapies for up to seven months after interruption or stopping of trastuzumab. If anthracyclines such as epirubicin are used, the patient's cardiac function must be carefully monitored.

If symptoms of cardiac failure develop during treatment with trastuzumab, following treatment with epirubicin hydrochloride, this must be treated with standard medical therapy.

Cardiac function must be carefully monitored in patients who take high cumulative doses and in those with risk factors. However, cardiotoxicity with epirubicin hydrochloride can occur with lower cumulative doses in the presence or absence of risk factors for cardiac toxicity.

There have been sporadic reports of foetal/neonatal cardiotoxic events, including foetal death, following in utero exposure to epirubicin (see section 4.6).

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

Haematological Toxicity Like with other cytotoxic agents, epirubicin can cause myelosuppression. The blood profile, including a differential WBC count, must be evaluated before and during each treatment cycle with epirubicin. Blood toxicity manifests mainly as reversible and dose-dependent leukopenia and/or granulocytopenia (neutropenia), which represent the most common manifestations of the acute dose-limiting toxicities of this medicinal products. Leucopoenia and neutropenia are usually more severe with high treatment doses, with the nadir occurring in most cases between the 10^{th} and 14^{th} day following administration of the drug; this is generally transient and the WBC/neutrophil counts return to normal within 21 days. Thrombocytopenia and anaemia may also occur. The clinical consequence of severe myelosuppression are: fever, infections, sepsis/septicaemia, septic shock, bleeding, tissue hypoxia, or death.

Secondary Leukaemia – There have been reports of secondary leukaemia, with or without a preleukaemic phase, in patients treated with anthracyclines, (including epirubicin). Secondary leukaemia is more common when these medicinal products are administered in combination with antineoplastic agents that damage DNA, in combination with radiotherapy, when patients have been heavily pre-treated with cytotoxic agents, or when doses of the anthracyclines have been increased. These leukaemia's can have a latency period that varies between one and three years. (See section 5.1).

Gastrointestinal tract - Epirubicin hydrochloride induces vomiting. Mucositis/stomatitis usually occur early after drug administration and, if severe, can progress in a few days to ulceration of the mucous membranes. In the majority of patients, recovery from these adverse events occurs within the third week of therapy.

Liver Function - The main route of elimination for epirubicin hydrochloride 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 for these patients (see sections 4.2 and 5.2). Patients with severe hepatic damage must not take epirubicin hydrochloride (see section 4.3).

Renal Function - Serum creatinine must be measured before and during therapy. A dose adjustment is necessary in patients with serum creatinine level > 5 mg/dL (see section 4.2).

Effects at Site of Injection **-** **I**njection into a small vessel or repeat injections in the same vein can cause phlebosclerosis. The risk of phlebitis/thrombophlebitis at the site of injection can be minimised by following the recommended administration procedures (see section 4.2).

Extravasation **-** Extravasation of epirubicin hydrochloride during intravenous injection can cause local pain, serious tissue injuries (onset of vesicles, severe cellulitis) and necrosis. If signs or symptoms of extravasation appear during an intravenous administration of epirubicin hydrochloride, the infusion of the medicinal product must be interrupted immediately. The undesirable effects resulting from extravasation of anthracyclines can be prevented or reduced by immediately using a specific treatment e.g. dexrazoxane (refer to the relevant product information for use of the product). The patient's pain can be alleviated by cooling the area and keeping it cold using hyaluronic acid and DMSO. The patient must be monitored carefully during the subsequent period as necrosis may occur several weeks after extravasation. A plastic surgeon should be consulted with a view to possible excision.

Other **-** Like with other cytotoxic agents, there have been reports of thrombophlebitis and thromboembolic events, including pulmonary embolism (in some cases fatal) with the use of epirubicin hydrochloride.

Tumour-Lysis Syndrome **-** Epirubicin hydrochloride can cause hyperuricemia as a consequence of the extensive catabolism of purines associated with the rapid tumour cell lysis induced by the medicinal product (tumour-lysis syndrome). Blood levels of uric acid, potassium, calcium phosphate, and creatinine must be measured after start of treatment. Hydration, alkalinisation of urine, and prophylaxis with allopurinol for preventing uric acid in blood can minimise the potential complications of tumour-lysis syndrome.

Immunosuppressant Effects/Increased Susceptibility to Infections- The administration of live vaccines or live-attenuated vaccines to patients immunosuppressed by chemotherapy agents, including epirubicin hydrochloride, can cause serious or fatal infections (see section 4.5).

Vaccination with live vaccines must be avoided in patients receiving epirubicin hydrochloride. Killed or inactivated vaccines can be administered; however, the response to these vaccines may be reduced.

Reproductive system: Epirubicin hydrochloride can cause genotoxicity. Men and women treated with epirubicin hydrochloride must use appropriate methods of contraception during treatment with epirubicin and for a certain period after completing treatment (see section 4.6). If appropriate and possible, patients who wish to have children after completion of therapy must request a genetic consultation.

Intravesical use - Administration of epirubicin hydrochloride can cause chemical cystitis symptoms (such as dysuria, polyuria, nocturia, stranguria, haematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Particular care must be paid to catheterisation problems (such as urethral obstruction caused by large intravesical tumours).

Intra-arterial route - Intra-arterial administration of epirubicin hydrochloride (transcatheter arterial embolisation for the localised 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) localised 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.

Excipient warning

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin hydrochloride can also be used in combination with other anticancer chemotherapy agents. Cumulative toxicity may manifest with effects on the bone marrow/blood and gastro-intestinal system (see section 4.4). The use of epirubicin hydrochloride in chemotherapy combined with other potentially cardiotoxic agents, as well as the concomitant use with cardioactive compounds (e.g., calcium channel blockers), requires cardiac function monitoring for the entire duration of treatment.

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

Anthracyclines including epirubicin, must not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is carefully monitored. Patients taking anthracyclines after the interruption or stopping of treatment with other cardiotoxic agents, particularly those with a long half-life such as trastuzumab, can also be exposed to an increased risk of onset of cardiotoxicity. Trastuzumab has a variable half-life and can remain in the circulatory system for up to seven months. Therefore, if possible, doctors must avoid an anthracycline-based therapy for up to seven months after the end of treatment with trastuzumab. If anthracyclines are used before this period, cardiac function must be monitored carefully.

Vaccination with live vaccines must be avoided in patients taking epirubicin hydrochloride. Killed or inactivated vaccines can be administered; however, the response to these vaccines may be reduced.

Cimetidine increases the AUC of epirubicin hydrochloride by 50% and the use of this medicinal product must be interrupted during treatment with epirubicin hydrochloride

When given prior to epirubicin hydrochloride, paclitaxel can cause increased plasma concentrations of unchanged epirubicin hydrochloride and its metabolites, the latter being, however, neither toxic nor active. Coadministration 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.

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

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

Quinine can accelerate the initial distribution of epirubicin hydrochloride from blood into the tissues and may influence the partitioning of red blood cells by epirubicin hydrochloride.

The co-administration of interferon α2b can cause a reduction in the terminal elimination half-life of both total and partial clearance of epirubicin hydrochloride.

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).

Patients who receive therapy in combination with anthracyclines and dexrazoxane may suffer an increase in myelosuppression.

Epirubicin may induce hyperuricaemia as a result of rapid lysis of neoplastic cells. If epirubicin is used concomitantly with other medicinal products which delay uric acid excretion (e.g. sulphonamides, certain diuretics), it may potentiate the hyperuricaemia.

Epirubicin is chemically incompatible with heparin; when both components are mixed, precipitation and loss of efficacy of both agents may occur (see section 6.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing age/contraception for men and women
Women of childbearing potential must be advised to avoid becoming pregnant during treatment and must use effective methods of contraception during treatment and for at least 7 months after last dose.

Men undergoing treatment with epirubicin hydrochloride must use effective contraceptive methods during treatment and for at least 4 months after last dose.

Pregnancy

There are limited data on the use of epirubicin in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Epirubicin should not be used during pregnancy unless the woman's clinical condition makes treatment with epirubicin necessary.

Avoid using epirubicin during the first trimester. Available human data do not establish the presence or absence of serious birth defects and miscarriage related to the use of epirubicin during the second and third trimesters.

Following in utero exposure to epirubicin during the second and/or third trimesters, sporadic cases of transient foetal and/or neonatal ventricular hypokinesia, transient increases in cardiac enzymes, and foetal death have been reported due to suspected anthracycline-induced cardiotoxicity (see section 4.4). Monitor the foetus and/or newborn for cardiotoxicity and perform testing consistent with local standards of care.

Fertility
Epirubicin hydrochloride could induce chromosomal damage in human spermatozoa. Men being treated with epirubicin hydrochloride should be advise to seek advice on the possibility of sperm conservation as the therapy may cause irreversible infertility.

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

Breast-feeding
It is not known whether epirubicin hydrochloride 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 hydrochloride, mothers should discontinue breastfeeding during treatment with epirubicin and for at least 7 days after the last dose.

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.

4.8 Undesirable effects

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

Over 10% of patients treated can develop undesirable effects. The most common undesirable effects are myelosuppression, gastrointestinal disorders, anorexia, alopecia and infections

System Organ Class	Very Common	Common	Uncommon	Rare	Not known
Infections and infestations	Infection, Conjunctivitis		Sepsis,* pneumonia*		Septic shock, Cellulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Acute myeloid leukaemia, Acute lymphocytic leukaemia		
Blood and lymphatic system disorders	Myelosuppression (Anaemia, Leukopenia, Neutropenia, granulocytopenia, Thrombocytopenia, Febrile neutropenia)				
Immune system disorders				Hypersensitivity[§], Anaphylactic reaction*	

Metabolism and nutrition disorders		Decreased appetite Dehydration*		Hyperuricaemia*	
Nervous system disorders		Burning sensation§		Dizziness	
Eye disorders	Keratitis				
Cardiac disorders		Ventricular tachycardia, Atrioventricular block, Bundle branch block, Bradycardia, congestive heart failure^		Cardiotoxicity‖	
Vascular disorders	Hot flushes, Phlebitis*	Bleeding*, Flushing*	Embolism, Embolism arterial,* Thrombophlebitis*		Shock*
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism*		Hypoxia**
Gastrointestinal disorders	Nausea, Vomiting, Stomatitis, Mucosal inflammation, Diarrhoea	Gastrointestinal pain,* Gastrointestinal erosion,* Oesophagitis Gastrointestinal ulcer*	Gastrointestinal haemorrhage*		Abdominal discomfort, oral mucosa erosion, Mouth ulceration, Oral pain, Burning sensation of the mucous membranes, Mouth haemorrhage,Pigmentation buccal*
Skin and subcutaneous tissue disorders	Alopecia, Skin toxicity	Rash/Pruritus, Nail pigmentation, * Skin disorder, Skin hyperpigmentation*	Urticaria* Erythema*		Photosensitivity reaction*
Renal and urinary disorders	Chromaturia*†	Pollakiuria§			
Reproductive system and breast disorders	Amenorrhoea			Azoospermia	
General disorders and administration site conditions	Malaise, Pyrexia*	Administration site erythema, Chills*	Asthenia		Phlebosclerosis, Pain, Soft tissue necrosisε
Investigations	Transaminases abnormal	Ejection fraction decreased			
Injury, poisoning and procedural complications	Chemical cystitis*§				Recall phenomenon*Δ

* ADR identified post-marketing.
** induced by myelosuppression
† Red coloration of urine for 1 to 2 days after administration.
ε following accidental paravenous injection
§ Following intravesical administration.
‖ e.g., ECG changes, arrhythmias, cardiomyopathy
Δ Hypersensitivity to irradiated skin (radiation-recall reaction).
^ (dyspnoea, oedema, hepatomegaly, ascites, pulmonary oedema, pleural effusion, gallop rhythm)

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 HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

An acute overdose with epirubicin hydrochloride can cause severe myelosuppression (mainly leucopoenia and thrombocytopenia), toxic gastrointestinal effects (mainly mucositis) and acute cardiac complications. Delayed cardiac failure has been observed with anthracyclines, which manifested from several months to years after completion of treatment (see section 4.4). Patients must be carefully monitored. If there are signs of cardiac failure, patients must be treated according to conventional guidelines.

Treatment:
Symptomatic. Epirubicin cannot be removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic antibiotics – anthracyclines.
ATC code: L01D B03.

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, breast cancer, Lewis lung carcinoma colon cancer (38) and also 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, epirubicin hydrochloride plasma levels after intravenous administration of 60-150 mg/m^2 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 hydrochloride and epirubicinol.

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

Epirubicin hydrochloride is eliminated mainly through the liver; high plasma clearance levels (0.9 l/min) show that the 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

The main target organs in rat, rabbit and dog following repeated dosing were the haemolymphopoietic system, GI tract, kidney, liver and reproductive organs.

Epirubicin hydrochloride was also cardiotoxic in the species tested.

It was genotoxic, and, like other anthracyclines, carcinogenic in rats.

Epirubicin hydrochloride was embryotoxic in rats. No malformations were seen in rats or rabbits, but like other anthracyclines and cytotoxic drugs, 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

Sodium Chloride
Hydrochloric acid (For pH adjustment)
Water for Injections

6.2 Incompatibilities

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

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

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

6.3 Shelf life

Shelf life of the product as package for sale:
2 year.

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 ºC-8 ºC). 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 20 mm chlorobutyl RTS rubber stopper and aluminium flip-off white seal.

25 ml vial: Type I tubular glass vial with 20 mm chlorobutyl RTS rubber stopper and aluminium flip-off white / royal blue seal.

50 ml vial: Type I clear moulded glass vial with 20 mm chlorobutyl RTS rubber stopper and aluminium flip-off royal blue seal.

100 ml vial: Type I clear moulded glass vial with 20 mm chlorobutyl RTS 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 and other handling

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 Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 11th January 2014

10 DATE OF REVISION OF THE TEXT

October 2023