Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin "EBEWE" 2mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml solution for injection or infusion contains 2mg Epirubicin hydrochloride
Each 5ml solution for injection or infusion contains 10mg Epirubicin hydrochloride
Each 25ml solution for injection or infusion contains 50mg Epirubicin hydrochloride
Each 50ml solution for injection or infusion contains 100mg Epirubicin hydrochloride
Each 100ml solution for injection or infusion contains 200mg Epirubicin hydrochloride

This medicinal product contains 0.154 mmol/ml (3.54 mg/ml) sodium
1 vial of 5 ml solution contains 0.77 mmol (17.70 mg) sodium
1 vial of 25 ml solution contains 3.85 mmol (88.52 mg) sodium
1 vial of 50 ml solution contains 7.70 mmol (177.02 mg) sodium
1 vial of 100 ml solution contains 15.40 mmol (354.05 mg) sodium

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Clear red solution for injection or infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Malignant neoplastic diseases:
Epirubicin has shown efficacy in breast cancer.
There is some evidence that indicate objective response in non-Hodgkin's lymphoma, breast-, ovarian-, gastric-, lungcancer and leukemias.

Intravesical administration of Epirubicin has been shown to be beneficial in superficial bladder cancer.

4.2 Posology and method of administration

Epirubicin is not active when given orally and should not be injected intramuscularly or intrathecally.

Adults and Children-Intravenous

Conventional doses
When Epirubicin is used as a single agent, the recommended dosage in adults is 60-120 mg/m^2 body surface area; the drug should be injected intravenously over 3-30 minutes. The dose should be repeated at 21-day intervals depending on the patient's haematomedullary status.

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

- Small cell lung cancer (previously untreated): 120 mg/m^2 day 1, every 3 weeks.
- Non-small cell lung cancer (squamous, large cell and adenocarcinoma previously untreated): 135 mg/m ^{2} on

Day 1 or 45 mg/m2 on Days 1, 2, 3 every 3-4 weeks.

Lower doses (60-75 mg/m^2 for conventional doses and 105-120 mg/m^2 for high doses) are recommended for patients whose bone marrow function has already 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.

When the drug is used in combination with other anti-tumour agents, the doses need to be adequately reduced. Since the major route of elimination of Epirubicin is the hepato-biliary system, the dosage should be reduced in patients with impaired liver function, in order to avoid an increase of overall toxicity. Moderate liver impairment (bilirubin:1.4-3 mg/100 ml), requires a 50% reduction of dose, while severe impairment (bilirubin> 3 mg/100 ml) necessitates a dose reduction of 75%.

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Epirubicin excreted by this route. While no specific dose recommendation can be made based on the limited available data in patients with renal impairment, lower starting doses should be considered in patients with severe renal impairment (serum creatinine >5 mg/dL).

It is advisable to give the drug via the tubing of a freely-running IV 0.9% saline or 5% glucose infusion after checking that the needle is well placed in the vein. This method minimises the risk of drug extravasation and makes sure that the vein is flushed with saline after the administration of the drug. Extravasation of Epirubicin from the vein during injection may give rise to severe tissue lesions, even necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Intravesical:
Intravesical administration of Epirubicin has been found to be beneficial in the treatment of superficial papillary transitional cell carcinoma of the bladder, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection. However, intravesical administration is not suitable for the treatment of invasive tumours which have penetrated the muscular layer of the bladder wall.

For the treatment of papillary transitional cell carcinoma of the bladder, a therapy of intermittent instillations (weekly for eight weeks) of 50 mg/50 ml is recommended.

In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg/50 ml is advised.
For carcinoma-in-situ, depending on the individual tolerability of the patient, the dose may be increased to 80 mg/50 ml. For prophylaxis of recurrences after transurethral resection of superficial tumours, intermittent administrations (weekly for four weeks) of 50 mg/ 50 ml followed by 11 monthly instillations at the same dosage are recommended.

Epirubicin, to be instilled using a catheter, should be retained intravesically for 1 hour. The patient should be instructed to void at the end of this time. To avoid any dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. During instillation, the pelvis of the patient should be rotated to ensure extensive contact of the solution with the vesical mucosa.

4.3 Contraindications

Hypersensitivity to epirubicin or any other component of the product listed in section 6.1, other anthracyclines or anthracenediones.
- Lactation

Intravenous use:
- persistent myelosuppression
- severe hepatic impairment
- severe myocardial insufficiency
- myocardiopathy
- 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

Intravesical use:

- urinary tract infections
- inflammation of the bladder
- hematuria
- invasive tumours penetrating the bladder
- catheterisation problems

4.4 Special warnings and precautions for use

General

Epirubicin "EBEWE" should be administered only under the supervision of a qualified physician experienced in antiblastic and cytotoxic therapy.

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

While treatment with high doses of epirubicin (e.g., $\geq$ 90 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 dose 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 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 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).

Cardiac function should be assessed before patients undergo treatment with epirubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of epirubicin 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/m^2 epirubicin should be exceeded only with extreme caution.

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 drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g. trastuzumab) (see section 4.5) with an increased risk 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 trastuzumab 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.

Haematologic Toxicity
As with other cytotoxic agents, epirubicin may produce myelosuppression. Haematologic profiles should be assessed before and during each cycle of therapy with epirubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leucopoenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopoenia and neutropenia are generally more severe with high-dose schedules, reaching the nadir in most cases between days 10 and 14 after drug administration; 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/septicaemia, septic shock, haemorrhage, tissue hypoxia, or death.

Secondary Leukaemia
Secondary leukaemia, with or without a preleukaemic phase, has been reported in patients treated with anthracyclines, including epirubicin. Secondary leukaemia 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. This leukaemia's can have a 1- to 3-year latency period. (See section 5.1).

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. Serum total bilirubin and AST levels should be evaluated before and during treatment with epirubicin. 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 during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. 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 using 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.

Tumor-Lysis Syndrome
Epirubicin may induce hyperuricemia because of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells (tumour-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumour-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 treated with epirubicin should adopt appropriate contraceptives 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, 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 (transcatheter arterial embolisation 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.

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

This medicinal product contains the following quantities of sodium per vial:

- 5 ml solution contains 0.77 mmol (17.70 mg) sodium
- 25 ml solution contains 3.85 mmol (88.52 mg) sodium
- 50 ml solution contains 7.70 mmol (177.02 mg) sodium
- 100 ml solution contains 15.40 mmol (354.05 mg) sodium

to be taken into consideration by patients on a controlled sodium diet

4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastro-intestinal effects (see section **4.4).** The use of epirubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment.

Epirubicin must not be diluted in alkaline infusion solutions (e.g. hydrogen carbonate solutions).

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

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.

Cimetidine increased the AUC of epirubicin by 50% and should be discontinued during treatment with epirubicin. When given prior to epirubicin, paclitaxel can cause increased plasma concentrations of unchanged epirubicin and its metabolites, the latter being, however, neither toxic nor active. Co-administration 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.
Dexverapamil may alter the pharmacokinetics of epirubicin and possibly increase its bone marrow depressant effects. 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.

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

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

Increase of myelosuppression may occur in patients receiving combination therapy of anthracycline and dexrazoxane.

4.6 Fertility, pregnancy and lactation

(See section 5.3)

Impairment of Fertility
Epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should use effective contraceptive methods and if appropriate and available, seek advice on sperm preservation due to the possibility of irreversible infertility caused by therapy. Epirubicin may cause amenorrhea or premature menopause in premenopausal women.

Pregnancy
Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and should use effective contraceptive methods. Experimental data in animals suggest that epirubicin may cause foetal harm when administered to a pregnant woman. 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 foetus.

There are no studies in pregnant women. Epirubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation
It is not known whether epirubicin is excreted in human 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, mothers should discontinue nursing prior to taking this drug.

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.

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 leukaemia, acute myelogenous leukaemia
Blood and the lymphatic system disorders	Very Common	Myelosuppression (leucopenia, granucytopenia and neutropenia, anemia and febrile neutropenia)
	Uncommon	Thrombocytopenia
	Not known	Haemorrhage and tissue hypoxia as 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, keratitis
Cardiac disorders	Rare	Congestive heart failure,(dyspnoea;

		oedema, hepatomegaly, ascites, pulmonary oedema, pleural effusions, gallop rhythm) cardiotoxicity (e.g. ECG abnormalities, arrhythmias, cardiomyopathy), ventricular tachycardia, bradycardia, AV block, bundle-branch block.
Vascular disorders	Common	Hot flashes, Hot flushes
	Uncommon	Phlebitis, thrombophlebitis
	Not known	Shock, thromboembolism, including pulmonary emboli
Gastrointestinal disorders	Common	Mucositis, esophagitis, stomatitis, vomiting, diarrhoea, nausea
	Not known	Oral mucosa erosion, mouth ulceration, oral pain, mucosal burning sensation, mouth haemorrhage, and buccal pigmentation
Skin and subcutaneous tissue disorders	Very Common	Alopecia
	Rare	Urticaria
	Not Known	Local toxicity, rash, itch, skin changes, erythema, flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction)
Renal and urinary disorders	Very common	Red coloration of urine for 1 to 2 days after administration
Reproductive system and breast disorders	Rare	Amenorrhea, azoospermia
General disorders and administration site conditions	Common	Infusion site erythema
	Rare	Malaise, asthenia, fever, chills
	Not Known	Phlebosklerosis, local pain, severe cellulitis, tissue necrosis after accidental paravenous injection
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: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Acute overdosage with epirubicin will result in severe myelosuppression (mainly leucopoenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications. Latent cardiac failure has been observed with anthracyclines several months to years after completion of treatment (see section 4.4). Patients must be carefully monitored. If signs of cardiac failure occur, patients should be treated according to conventional guidelines.

Treatment:
Symptomatic Epirubicin cannot be removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: L01D B 03

Epirubicin is an anthracycline cytotoxic agent. Although it is known that anthracyclines can interfere with a number of biochemical and biological functions within eukaryotic cells, the precise mechanisms of epirubicin's cytotoxic and/or antiproliferative properties have not been completely elucidated.

Epirubicin forms a complex with DNA by intercalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acid (DNA and RNA) and protein synthesis. Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity. Epirubicin also inhibits DNA helicase activity, preventing the enzymatic separation of double-stranded DNA and interfering with replication and transcription. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicals. The antiproliferative and cytotoxic activity of Epirubicin is thought to result from these or other possible mechanisms.

Epirubicin is cytotoxic *in vitro* to a variety of established murine and human cell lines and primary cultures of human tumours. It is also active *in vivo* against a variety of murine tumours and human xenografts in athymic mice, including breast tumours.

5.2 Pharmacokinetic properties

Epirubicin is metabolised in the liver and excreted mainly via the bile with $t_{1/2}$ of 40 hours.

Epirubicin pharmacokinetics are linear over the dose range of 60 to 150 mg/m and plasma clearance is not affected by the duration of infusion or administration schedule.

Distribution: Following intravenous administration, Epirubicin is rapidly and widely distributed into the tissues. Binding of Epirubicin to plasma proteins, predominantly albumin, is about 77% and is not affected by drug concentration. Epirubicin also appears to concentrate in red blood cells; whole blood concentrations are approximately twice those of plasma.

Metabolism: Epirubicin is extensively and rapidly metabolized by the liver and is also metabolized by other organs and cells, including red blood cells. Four main metabolic routes have been identified:
(1) reduction of the C-13 keto-group with the formation of the 13(S)-dihydro derivative, epirubicinol;

(2) conjugation of both the unchanged drug and epirubicinol with glucuronic acid;
(3) loss of the amino sugar moiety through a hydrolytic process; and
(4) loss of the amino sugar moiety through a redox process

Epirubicinol has in vitro cytotoxic activity one-tenth that of epirubicin. As plasma levels of epirubicinol are lower than those of the unchanged drug, they are unlikely to reach *in vivo* concentrations sufficient for cytotoxicity. No significant activity or toxicity has been reported for the other metabolites.

Excretion: Epirubicin and its major metabolites are eliminated through biliary excretion and, to a lesser extent, by urinary excretion. Mass-balance data from 1 patient found about 60% of the total radioactive dose in faeces (34%) and urine (27%). These data are consistent with those from 3 patients with extrahepatic obstruction and percutaneous drainage, in whom approximately 35% and 20% of the administered dose were recovered as Epirubicin or its major metabolites in bile and urine, respectively, in the 4 days after treatment.

Pharmacokinetics in Special Populations

Hepatic Impairment:
Epirubicin is eliminated by both hepatic metabolism and biliary excretion and clearance is reduced in patients with hepatic dysfunction.

The median plasma clearance of Epirubicin was decreased compared to patients with normal hepatic function by about 30% in patients with elevated AST but normal bilirubin, and by 50% in patients with elevations of both AST and bilirubin. Patients with more severe hepatic impairment have not been evaluated (see Sections 4.2 Posology and Method of administration and 4.4 Special warnings and precautions for use).

Renal Impairment:
No significant alterations in the pharmacokinetics of epirubicin or its major metabolite, epirubicinol, have been observed in patients with serum creatinine < 5 mg/dL. A 50% reduction in plasma clearance was reported in four patients with serum creatinine 25 mg/dL (see Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use). Patients on dialysis have not been studied.

5.3 Preclinical safety data

Epirubicin has been shown to be carcinogenic in animals. The possibility of similar effect should be borne in mind when designing the long term management of the patient. Epirubicin is mutagenic and clastogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid
Water for injections

6.2 Incompatibilities

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug. Epirubicin should not be mixed with heparin due to chemical incompatibility which may lead to precipitation when the drugs are in certain proportions.

Epirubicin solution for injection or infusion must not be mixed with other preparations except with those mentioned in 6.6.

6.3 Shelf life

Unopened: 2 years. The product should be used immediately after opening.

Remove solution from vial immediately before use. From a microbiological point of view, the product should be used immediately after 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 longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Tests of the diluted solution up to 96 hours at 2-8°C and room temperature (20-25°C) show no significant changes without protection from light.

6.4 Special precautions for storage

Store at 2°C to 8°C.

For storage conditions after first opening of the medicinal product, see section 6.3.

Storage of the medicinal product at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after 2 to a maximum of 4 hours equilibration at controlled room temperature (15° to 25°C)

6.5 Nature and contents of container

Clear vials of glass Type I PhEur with fluoropolymer coated halobutyl rubber stoppers and crimp cap of a nominal capacity of 5ml, 25ml, 50ml, and 100ml.

Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Recommended infusion solutions are Sodium Chloride Intravenous Infusion 0.9% w/v, Glucose Intravenous Infusion 5% w/v or Sodium Chloride and Glucose Intravenous Infusion.

Preparation of solution for infusion must take place in aseptic conditions.

The following protective recommendations are given due to the toxic nature of this substance.
-Personnel should be trained in good technique for reconstitution and handling.
-Pregnant staff should be excluded from working with this drug.
-Personnel handling epirubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
-A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed, absorbent paper.
-all items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk, waste-disposal bags for high temperature incineration.

Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution; medical attention should be sought.

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 indicated previously.

Handle according to the guidelines for cytostatics

7 MARKETING AUTHORISATION HOLDER

Fannin Limited
Fannin House

South County Business Park
Leopardstown
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1457/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation 17th February 2006

Date of Last Renewal 17th February 2011

10 DATE OF REVISION OF THE TEXT

May 2015