Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

EPI-cell® 50 mg
2 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial with 25 ml solution for injection contains 50 mg epirubicin hydrochloride.

Excipient(s) with known effect
1 vial contains 85 mg sodium.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, dark-red solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of a wide spectrum of neoplastic diseases including breast carcinoma, lung carcinoma (high doses), ovarian carcinoma, gastric carcinomas, soft tissue sarcoma.

Intravesical administration of epirubicin has been found to be beneficial in the treatment of superficial bladder carcinomas and in the prophylaxis of recurrences after transurethral resection.

IV administration for the treatment of advanced bladder carcinoma.

4.2 Posology and method of administration
Epirubicin injection is administered to patients by intravenous infusion. Epirubicin is given in repeated 3 to 4-week cycles. The total dose of epirubicin may be given on Day 1 of each cycle or divided equally and given on Days 1 and 8 of each cycle. To minimize the risk of thrombosis or perivenous extravasation. The usual infusion times range between 3 and 20 minutes depending upon dosage and volume of the infusion solution. The needle should be properly placed in the vein. This reduces the risk of thrombosis and extravasation that could lead to severe cellulitis and necrosis. In case of extravasation, administration should be stopped immediately. Injection in small veins and repeated injection in the same vein can lead to venous sclerosis.

The recommended dosages of epirubicin are as follows:
Starting Doses
The recommended starting dose of epirubicin is 60 to 120 mg/m². The following regimens were used in trials supporting use of epirubicin as a component of adjuvant therapy in patients with axillary-node positive breast cancer

CEF-120*	Cyclophosphamide	75 mg/m² PO D 1-14
	Epirubicin	60 mg/m² IV D 1, 8
	5-Fluorouracil	500 mg/m² IV D 1, 8
	Repeated every 28 days for 6 cycles	

FEC-100**:	5-Fluorouracil	500 mg/m²
	Epirubicin	100 mg/m²

Cyclophosphamide	500 mg/m²

* Study evaluating epirubicin 120 mg/m² per course in combination with cyclophosphamide and fluorouracil.
** Study evaluating epirubicin 100 mg/m² per course in combination with fluorouracil and cyclophosphamide.
All drugs administered intravenously on Day 1 and repeated every 21 days for 6 cycles.
Patients administered the 120-mg/m² regimen of epirubicin also received prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole, or a fluoroquinolone.

Bone Marrow Dysfunction
Consideration should be given to administration of lower starting doses (75-90 mg/m²) for heavily pretreated patients, patients with pre-existing bone marrow depression, or in the presence of neoplastic bone marrow infiltration.

Hepatic Dysfunction
Definitive recommendations regarding use of epirubicin in patients with hepatic dysfunction are not available because patients with hepatic abnormalities were excluded from participation in adjuvant trials of FEC-100/CEF-120 therapy (in patients with elevated serum AST or serum total bilirubin concentrations, the following dose reductions were recommended in clinical trials, although few patients experienced hepatic impairment:
Bilirubin 1.2 to 3 mg/dL or AST 2 to 4 times upper limit of normal 1/2 of recommended starting dose
Bilirubin > 3 mg/dL or AST >4 times upper limit of normal 1/4 of recommended starting dose.

Renal Dysfunction
While no specific dose recommendation can be made based on the limited available data in patients with renal impairment, lower doses should be considered in patients with severe renal impairment (serum creatinine > 5 mg/dL).

High starting dose regimens
High starting doses of epirubicin may be used in the treatment of breast and lung cancer. As a single agent, the recommended high starting dose of epirubicin per cycle in adults (up to 135 mg/m²) should be administered on day 1 or in divided doses on days 1, 2, 3, every 3 to 4 weeks. In combination therapy, the recommended high starting dose (up to 120 mg/m²) should be administered on day 1, every 3 to 4 weeks.

Dose Modifications
Dosage adjustments after the first treatment cycle should be made based on hematologic and nonhematologic toxicities. Patients experiencing during treatment cycle nadir platelet counts <50,000 mm3, absolute neutrophil counts (ANC) <250/mm3, neutropenic fever, or Grades 3/4 nonhematologic toxicity should have the Day 1 dose in subsequent cycles reduced to 75% of the Day 1 dose given in the current cycle. Day 1 chemotherapy in subsequent courses of treatment should be delayed until platelet counts are ≥100,000/ mm3, ANC ≥1500/mm3, and nonhematologic toxicities have recovered to ≤Grade 1.
For patients receiving a divided dose of epirubicin (Day 1 and Day 8). The Day 8 dose should be 75% of Day 1 if platelet counts are 75,000-100,000/mm3 and ANC is 1000 to 1499/mm3. If Day 8 platelet counts are <75,000/mm3, ANC <1000/mm3, or Grade 3/4 nonhematologic toxicity has occurred, the Day 8 dose should be omitted.

Intravesical Administration
Epirubicin should be instilled using a catheter and retained intravesically for 1 hour. During instillation, the patient should be rotated to ensure that the vesical mucosa of the pelvis recelvos the most extensive contact with the solution. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. The patient should be instructed to void at the end of the instillation.
Intravesical administration is not suitable for the treatment of invasive tumors which have penetrated the muscular layer of the bladder wall.

Superficial bladder tumors
Single instillation: A single instillation of 80-100 mg immediately following transurethral resection (TUR) is recommended.

4-8 weeks course followed by monthly instillation: Eight weekly instillations of 50 mg (in 25-50 ml of saline solution) starting 2-7 days following TUR are recommended. In the case of local toxicity

(chemical cystitis), the dose should be reduced to 30 mg. Patients may receive 4 weekly administrations of 50 mg followed by 11 monthly instillations at the same dosage.

4.3 Contraindications

- Hypersensitivity to the active substance, other anthracyclines/anthracenediones or to any of the excipients listed in section 6.1
- Lactation (see section 4.6)

Intravenous administration
- 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
- myocardiopathy
- acute inflammatory heart diseases

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

If there is urinary backflow from the bladder to the renal pelvis (vesicorenal reflux) regular monitoring of the kidney function is necessary.

4.4 Special warnings and precautions for use

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

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

While treatment with high doses of epirubicin hydrochloride (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.

<u>Early (i.e., Acute) Events</u>
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 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 CHF or a cardiomyopathy increases rapidly with increasing total cumulative doses of epirubicin hydrochloride in excess of 900 mg/m^2; this cumulative dose should only be exceeded with extreme caution.

Cardiac function should be assessed before patients undergo treatment with epirubicin and must be monitored throughout therapy to minimise 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.

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 trastuzumab 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 28 - 38 days, trastuzumab may persist in the circulation for up to 27 weeks after stopping trastuzumab treatment. Patients who receive anthracyclines such as epirubicin after stopping trastuzumab may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab. If anthracyclines such as epirubicin 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 leucopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopenia 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. These leukaemias can have a 1- to 3-year latency period.

Gastrointestinal
Epirubicin is emetogenic. 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 patient’s pain may be relieved by cooling down the area and cooling for 24 hours. The patient should be monitored closely during the subsequent period of time, as necrosis may occur after several weeks. Should necrosis occur due to extravasation 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
Epirubicin may induce hyperuricaemia 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 alkalinisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimise 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).

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.

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 catheterisation problems (e.g. urethral obstruction due to massive intravesical tumours).

Excipients
EPI-cell® contains 85 mg sodium per vial, equivalent to 4.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 concurrent administration of epirubicin and other cardiotoxic drugs (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes) or concomitant (or prior) radiotherapy of the mediastinum increase the cardiotoxicity of epirubicin.
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 is extensively metabolised 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).

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 between 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

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. 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.

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

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

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. Men, who are treated with epirubicin, should not farther a child during treatment and up to 6 months thereafter.
Epirubicin may cause amenorrhoea or premature menopause in premenopausal women.

Pregnancy
Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and up to 6 months thereafter 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. 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 form the available data).

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

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 lymphatic system disorders	Very Common	Myelosuppression (leucopenia, granulocytopenia and neutropenia, anaemia and febrile neutropenia)
	Uncommon	Thrombocytopenia
	Not known	Haemorrhage and tissue hypoxia as result of myelosuppression.
Immune system disorders	Rare	Anaphylaxis (anaphylactic/anaphylactoid reactions with or without shock)
Metabolism and nutrition disorders	Common	Anorexia, dehydration
	Rare	Hyperuricaemia (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
	Uncommon	Phlebitis, thrombophlebitis
	Not known	Shock, thromboembolism, including pulmonary emboli

Gastrointestinal disorders	Common	Mucositis, oesophagitis, stomatitis, characterised by pain, burning sensation, erosions, ulcerations, bleeding; 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	Amenorrhoea, azoospermia
General disorders and administration site conditions	Common	Infusion site erythema
	Rare	Malaise, asthenia, fever, chills
	Not known	Phlebosclerosis, localpain, severe cellulitis, tissue necrosis after accidental paravenous injection
Investigations	Rare	Changes in transaminase levels
	Not Known	Asymptomatic drops in left ventricular ejection fraction

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
Secondary acute myeloid leukaemia with or without a pre-leukaemic phase, in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents has been observed.
These leukaemias have a short (1-3 year) latency.

Blood and the lymphatic system disorders:
High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumours and have caused adverse events which are not different from those seen at conventional doses with the exception of reversible severe neutropenia (< 500 neutrophils/mm^3 for < 7 days) which occurred in the majority of patients. Only few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.

Skin and subcutaneous tissue disorders:
Alopecia, normally reversible, appears in 60-90% of treated patients; it is accompanied by lack of beard growth in males.

General disorders and administration site conditions
Mucositis - may appear 5-10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, ulceration and bleeding, mainly along the side of the tongue and the sublingual mucosa.

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

<u>Undesirable effects after intravesical administration</u>:

As only a small amount of active ingredient is reabsorbed after intravesical instillation, severe systemic adverse drug reactions are rare. Systemic side effects may occur in isolated cases during early start of instillation (within 24 hours after TUR), extensive tumour infestation of the bladder or bladder inflammation. Local side effects may if necessary be reduced by decreasing the concentration of the instillment (up to 1 mg/ml) within the given dosing recommendations or alternatively by prolonging the treatment interval.

Local undesirable effects after intravesical administration:
Common: Chemical cystitis (approx. 20%) in combination with dysuria, pain and uncommonly haematuria. Bacterial cystitis (approx. 17%) may occur, due to application, e.g. unsterile catheters.
Rare: allergic reactions.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Acute overdosage with epirubicin will result in severe myelosuppression (mainly leucopenia and thrombocytopenia) within 10-14 days, gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications (within 24 hours). 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.

Management
Symptomatic. Epirubicin cannot be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antibiotic with a cytostatic effect belonging to the group of anthracyclines
ATC code: L01D B03

Epirubicin is a 4'-epimer of the anthracycline antibiotic doxorubicin. Its pharmacological properties correspond to those of other anthracyclines. Epirubicin is active during all phases of the cell cycle and demonstrates maximum cytotoxic effects in the S and G_2 phase of the cell cycle. The exact antineoplastic mode of action is not completely known, but is most likely based on its ability to form complexes with DNA by intercalating between DNA base pairs. This leads to steric inhibition of DNA and RNA synthesis.

The intercalation of epirubicin also appears to interfere with the topoisomerase DNA "cleavable complex". Further modes of action presently discussed are the formation of free radicals, a direct membrane effect, as well as the formation of chelates with metal ions.

Epirubicin is active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcoma SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also proved effective against human tumours transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

5.2 Pharmacokinetic properties

Shortly after IV application, epirubicin concentrations are found in most tissues. In spite of the large volume of distribution of epirubicin, experimental tests on animals show that epirubicin crosses the blood-brain barrier only to a very limited extent.

Epirubicin plasma levels follow a tri-exponential decreasing pattern with a rapid initial distribution phase ($t_{1/2\alpha}$: 3.0-4.8 minutes), followed by an intermediate elimination phase ($t_{1/2\beta}$: 1.1-2.6 hours) and a slow terminal phase of elimination ($t_{1/2\gamma}$: 18 – 45 hours).

The volume of distribution (Vd) of epirubicin is 32 – 46 l/kg.
Plasma clearance ranges from 30 – 100 l/h.

Epirubicin is mainly metabolised in the liver. One active metabolite (epirubicinol) and 6 inactive metabolites (epirubicinol glucuronide, epirubicin glucuronide as well as 4 aglycones) have been identified. Epirubicinol demonstrates a ten times lower cytotoxic activity in vitro than epirubicin. No significant activity or toxicity could be detected for the other metabolites.

Approximately 6 – 7% of an administered dose is eliminated in unchanged form via the kidneys, less than 5% as glucuronides and even smaller amounts as epirubicinol. Following hepatic metabolisation, approx. 35% of an administered dose is eliminated via biliary excretion. The biliary and renal clearance are 8 – 33 and 4 – 15 l/h respectively.

5.3 Preclinical safety data

Acute toxicity / Chronic toxicity
The changes observed in animals in the course of acute and chronic toxicity studies resemble the clinical side effects that are observed in patients.

Mutagenic/carcinogenic potential
Mutagenic effects for epirubicin have been proved in several tests. Animal experiments have shown epirubicin to have a cancerogenic effect.

Teratogenesis/Reproductive toxicology
Epirubicin has toxic effects on reproduction both in vivo and in vitro; it has embryotoxic effects on rats. In rats and rabbits no malformations were observed; however, like other anthracyclines and cytostatic agents, epirubicin has to be considered as potentially teratogenic.

Tests on rabbits showed, at a dose of 0.1 and 0.2 mg of epirubicin hydrochloride/kg/day, no significant differences in the parameters for teratogenesis compared to the control group; at doses of 0.4 mg of epirubicin hydrochloride/kg/day, extreme toxicity with a high mortality rate of dams and numerous miscarriages was shown.

After repeated doses, atrophy of the testes, especially of the tubuli, and disturbance of spermatogenesis were observed in rats and dogs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium-(S)-lactate-solution (50%) and hydrochloric acid 36% for buffering, water for injections

6.2 Incompatibilities

Due to chemical incompatibilities EPI-cell® should not be mixed with heparin. If EPI-cell® is administered concomitantly with other cytostatic drugs, they should not be directly mixed with each other. EPI-cell® should neither be brought into contact with any solution of alkaline pH (hydrolysis).

6.3 Shelf life

The expiry date is indicated on the packaging materials.

Chemical and physical in-use stability after dilution in 5% glucose solution or 0.9% sodium chloride solution has been demonstrated for 2 weeks at 2°C to 8°C and at 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Keep the vial in the outer carton in order to protect the content from light.

6.5 Nature and contents of container

Clear vials (glass type I) with chlorobutyl stopper and aluminium cap with plastic flip-off top.

Pack of 1vial containing 25 ml solution for injection.

6.6 Special precautions for disposal and other handling

Discard any remaining contents after use.

Instructions for use and handling
EPI-cell® is a ready-to-use solution and has a pH of 2.5 – 3.5. Prior to administration, the solution should be brought up to room temperature. EPI-cell® contains no preservatives and is therefore not intended for multiple-dose usage.

Prior use the solution for injection must be free of particles. Solutions for injection, which contain particles, must not be used and must be disposed in accordance to the current guidelines for cytostatic agents.

When handling EPI-cell®, appropriate precautionary measures should be taken, as with all similar cytotoxic substances (contact with skin and mucosae should be avoided).

Personnel handling EPI-cell® must wear protective clothing. Should EPI-cell® come into contact with skin or mucosae, careful cleaning with water and soap is recommended. Contact with the skin or eyes should be treated immediately by copious lavage with water or water and soap or sodium bicarbonate solution, and medical attention should be sought.

Instructions for the removal of any unused solution
Any unused EPI-cell® and all materials which have come into contact with EPI-cell® must be correctly disposed in accordance to the current guidelines for cytostatic substances.

7. MANUFACTURER

STADAPHARM GmbH
Stadastraße 2-18
61118 Bad Vilbel
Germany

8. REGISTRATION HOLDER

MBI Pharma Ltd.

P.O.B 5061,
Kadima

Israel

9. MARKETING AUTHORISATION NUMBER

155-92-34259-00

Revised in June 2021 according to MOH guidelines