SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Epirubicin HCl Karma 2mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 25ml vial contains:
Epirubicin Hydrochloride …. 50mg
3. PHARMACEUTICAL FORM
Solution for Injection
A clear red solution.
4.1 Therapeutic indications

- breast cancer
- advanced ovarian cancer
- gastric cancer
- small cell lung cancer
- soft-tissue sarcoma

4.2 Posology and method of administration

Posology
1. Conventional dosage
Interval therapy with 75-90 mg epirubicin hydrochloride/m² body surface area as a single dose every third week.
2. Combination therapy
When combining epirubicin hydrochloride and other cytostatic agents with potential overlapping toxicity, the dose must be reduced accordingly.
Dose reduction (60-75 mg epirubicin hydrochloride/m² body surface or 105-120 mg epirubicin hydrochloride/m² body surface with dose-intensified schemes) or longer intervals between should be considered in patients whose bone marrow function has been impaired by previous chemotherapy or radiotherapy, by age or neoplastic bone marrow infiltration.
To reduce side effects in palliative therapy or in patients in whom epirubicin hydrochloride cannot be administered in the dosage mentioned above for medical reasons, the following dosage may be applied:
- with 20-30 mg epirubicin hydrochloride/m² body surface area, weekly
3.1 High dose therapy for treatment of advanced small cell lung cancer
Interval therapy with 120 mg epirubicin hydrochloride/m² body surface area as a single dose every third week.
Special Note:
In patients whose bone marrow function has been impaired by previous chemotherapy or radiotherapy or neoplastic bone marrow infiltration a dose reduction to 105 mg epirubicin hydrochloride/m² body surface area is recommended.
3.2 High dose therapy at breast cancer (no standard therapy) for:

- treatment of advanced breast cancer:
  135 mg epirubicin hydrochloride/m² body surface area in monotherapy or 120 mg epirubicin hydrochloride/m² body surface area in combination therapy every 3-4 weeks.

- adjuvant treatment of early breast cancer patients with positive lymph nodes:
  100-120 mg epirubicin hydrochloride/m² body surface area every 3-4 weeks.

Both in the adjuvant therapy as well as in the treatment of metastatic breast cancer, the haematological and cardiac parameters as well as the organ functions should be monitored.
Careful hematologic monitoring is necessary, since a bone marrow depression is more frequent in patients under high dose treatment.
Severe neutropenia (neutrophils less than 500/µl for a maximum of 7 days) was usually observed 10-14 days after start of treatment and is usually temporary. In general, the bone marrow function recovers until day 21. Because of this short time, usually only a few patients need treatment in a hospital or treatment of serious infections.
Thrombocytopenia (platelet count below 100,000/µl) occurs only in a few patients and is rarely severe.

Patients with impaired liver function
The major route of elimination of epirubicin hydrochloride is the hepatobiliary system. In impaired liver function or biliary drainage disorders delayed elimination of the drug may occur, which will increase the overall toxicity. Therefore, liver function (bilirubin, SGOT, SGPT, alkaline phosphatase) should be checked before treatment with epirubicin. In patients with impaired liver function the dose should be reduced based on serum bilirubin levels as follows:

Serum Bilirubin	Dose Reduction
1,2-3,0 mg/100 ml	50 %
3,1-5,0 mg/100 ml	70 %

Patients with impaired renal function
Due to insufficient data for patients with impaired renal function, it is not possible to give special dose recommendations. In single cases it should be considered for patients with severe impaired renal function (glomerular filtration rate <10 ml/min or serum creatinine >5 mg/dl) to receive a dose reduction of initial dose of 75%.

Method of administration
Treatment should only be carried out by physicians who are experienced in the treatment of tumours, in a clinic or in cooperation with a hospital. In particular, the dose-intensified treatment requires close monitoring of patients because of possible complications due to strong myelosuppression. The application is strictly carried out according to regulations.

Before treatment with epirubicin laboratory values and cardiac function should be carefully examined; during each cycle of treatment, patients should be carefully and regularly.

The duration of treatment depends on the treatment protocol. There is no time limit.

The cumulative maximum dose (900 mg epirubicin hydrochloride/m² BSA) may be exceeded after benefit/risk assessment only.

Intravenous administration

<Intended name> must be administered intravenously. Accidental intraarterial or perivenous administration during systemic use must be excluded. Epirubicin HCl Karma 2mg/ml solution for injection is not intended for oral, subcutaneous, intramuscular or intrathecal use.
As perivenous injection cause severe necrosis it is recommended to administer Epirubicin HCl Karma 2mg/ml solution for injection via the tubing of a freely running intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution or glucose 50 mg/ml (5%) solution. To check that the needle is properly placed in the vein, infuse some ml of the infusion solution before epirubicin hydrochloride is injected.
The total amount of Epirubicin HCl Karma 2mg/ml solution for injection is administered intravenously within 10-15 minutes. Sclerosis may be caused by injection in to small veins or repeated injections in the same vein. After administration, the vein is rinsed with infusion solution.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 ,
- Severe myelosupression due to (pre)treatment with other neoplastic drugs or radiotherapy
- Severe inflammation of oral and/or gastrointestinal mucosa
- Acute systemic infections
- Severe hepatic impairment
- Acute or recent myocardial insufficiency in the patient's history (including myocardial insufficiency stage IV, acute or recent myocardial infarction which caused a myocardial insufficiency stage III or IV, cardiomyophaty, acute inflammatory heart disease, instable angina pectoris, arrhythmia with severe hemodynamic consequences
- previous treatments with maximum cumulative doses of other anthracyclines like doxorubicin or daunorubicin
- Lactation

Patients with other stages of the listed heart disease and/or pre-treatment with other anthracyclines require an individual therapeutic decision, including the following controls.
Note:
Special care is required for patients under previous, simultaneous or planned radiotherapy as the risk of local reaction at the field of radiation may occur (radiation recall).
A previous radiation of the mediastinum increases the risk of epirubicin induced cardiotoxicity
A cardiac monitoring is recommended when epirubicin doses above 450 mg / m^2 BSA; the maximum cumulative dose should not exceed 900 mg/m^2 BSA.

Before starting treatment with epirubicin, the patient should be recovered from the toxic effects (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) of a previous cytotoxic treatment.
Vaccination with live vaccines should not be performed in temporal association with epirubicin therapy.
The contact of the patient with polio vaccinees should be avoided.
Epirubicin HCl Karma 2mg/ml solution for injection must not be administered orally, subcutaneously, intramuscularly or intrathecally.

4.4 Special warnings and precautions for use

General
The drug should only be administered under the supervision of doctors with special knowledge in the therapy with cytotoxic.

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. During treatment with high doses of epirubicin hydrochloride special attention must be paid to possible clinical complications caused by profound myelosuppression**.**

Cardiac function
Cardiotoxicity is a risk of anthracyclines treatment. This may be manifested by early (i.e. Acute) or late (i.e. Delayed) events.

Early events
Early cardiotoxicity of epirubicin consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia as well as atrioventricular and bundle- branch block, have also been reported.
These effects are not usually predictive of the subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not considered to be a reason for discontinuing epirubicin treatment.

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

The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin hydrochloride in excess of 900 mg/m^2. This cumulative dose should only exceed 900 mg/m^2 with extreme caution.

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

The risk of developing CHF may be decreased by regular monitoring of LVEF during course of treatment. Treatment should be discontinued immediately at the first sign of impaired cardiac function.
The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). It is recommended to assess cardiac function with an ECG and either a MUGA scan or an ECHO before starting treatment, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracyclines doses. The technique used for assessment should also be used consistently throughout follow-up.

Given the risk of cardiomyopathy, the cumulative dose of 900 mg/m^2 should not be exceeded.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other medicinal products with the ability to suppress cardiac contractility or cardiotoxic medicinal products (e.g. trastuzumab) with an increased risk in the elderly. Concomitant treatment with other cardiotoxic medicine and anthracyclines such as epirubicin should be avoided unless the cardiac function is monitored.

Moderate severe heart failure (New York Heart Association [NYHA] class II-IV), in some cases associated with death, has been observed in patients receiving trastuzumab therapy alone or in combination with epirubicin.

Concurrent treatment with trastuzumab and anthracyclines such as epirubicin should be avoided except in clinical trials with cardiac monitoring. Patients treated with trastuzumab who have previously received anthracyclines are also at risk of cardiotoxicity, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.

A half-life of 28-38 days means that trastuzumab can be presented for up to 27 weeks after completion of treatment. Patients who receive treatment with anthracyclines such as epirubicin after stopping trastuzumab could be at increased risk of cardiotoxicity. Treatment with anthracyclines should be avoided for up to 27 weeks after completion of treatment with trastuzumab. If anthracyclines such as epirubicin are used, the patient's cardiac function should be closely monitored.
Cardiac failure during trastuzumab therapy subsequent to epirubicin must be treated with standard medical care.

Cardiac function should be carefully monitored 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.
The toxicity of epirubicin and other anthracyclines or anthracenediones may be additive

Haematological toxicity

As with other cytotoxic agents, epirubicin may cause myelosuppression. The complete blood count should be monitored before and during treatment cycles with epirubicin, including differential white blood cell (WBC) counts.
Dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of hematologic toxicity and is the most common dose limiting factor.
Leukopenia and neutropenia are most severe 10-14 days after treatment. In the majority of cases, the values return to normal 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 preleukemic phase, has been reported in patients treated with anthracyclines (including epirubicin). Secondary leukaemia is more common when such medicinal products are given in combination with other DNA-damaging antineoplastic agents, combined with radiation treatment, when patients have been heavily pre-treated with cytotoxic medicinal products, or when doses of anthracyclines have been escalated. These types of leukaemia can have 1-3 years latency period.

Gastrointestinal effects

Vomiting can occur during treatment with epirubicin. Mucositis and stomatitis generally appear early on after administration of the medicinal product and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover by the third week of therapy.

Liver function

Epirubicin is eliminated mainly through the hepatobiliary system. Total serum bilirubin and ASAT levels should be measured before and during treatment with epirubicin. In patients with elevated bilirubin or ASAT the clearance of the medicinal product may be slower with an increase in overall toxicity. Lower doses are recommended in these patients. Patients with severe hepatic impairment should not receive epirubicin.

Renal function

Serum creatinine should be assessed before and during treatment with epirubicin. Dose adjustment is necessary in patients with serum creatinine >5 mg/dl.

Effects at the site of injection

Phlebosclerosis may result from injection into a small vessel or from repeated injections into the same vein.

By following the recommended administration procedure, the risk of phlebitis/thrombophlebitis at the injection site can be minimized.

Extravasation

Extravasation of epirubicin during injection may cause local pin, severe tissue lesions (vesication, severe cellulitis) and necrosis. Should symptoms of extravasation occur during intravenous administration of epirubicin, the infusion should be discontinued immediately. The adverse effect of extravasation may be prevented or reduced by immediately initiating treatment with dexrazoxane (follow the treatment instructions for dexrazoxane). The patient's pain may be relieved by cooling the area, use of hyaluronic acid and dimethyl sulfoxide. The patient should be monitored closely thereafter, as necrosis may develop after several weeks. If extravasation occurs, a plastic surgeon should be consulted with a view to possible excision.

Other

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

Tumour-lysis syndrome

Epirubicin may induce hyperuricemia due to the extensive purine catabolism that accompanies rapid lysis of neoplastic cells (tumour-lysis syndrome). Serum carbamid, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinisation, and prophylaxis with allopurinol to prevent hyperuricemia may minimize the potential complications of tumour-lysis syndrome.

Immunosuppressive effects/increased susceptibility to infections

Administration of live or attenuated vaccines should be avoided in patients immunocompromised by chemotherapeutic agents, including epirubicin, as serious or fatal infections may result. The use of live vaccines 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 have genotoxic effects. Men and women treated with epirubicin should use appropriate contraceptives during treatment.

Advice on sperm banking prior treatment with epirubicin is recommended due to the risk of drug-induced infertility.

Patients wishing to have children after completion of therapy should be advised to first seek genetic counselling.

This medicinal product contains less than 1 mmol sodium (23 mg) per 1 ml, i.e. essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin is mainly used in combination with other cytotoxic medicinal products. Additive toxicity may occur especially with regard to bone marrow/hematologic and gastrointestinal effects.
Cardiac function must be monitored throughout treatment if epirubicin is combined with other potential cardiotoxic medicinal products (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxans) or radiation therapy of the mediastinum. Therefore, in this case as well as under concomitant use of other cardioactive substances (e.g. calcium antagonists), extra monitoring of cardiac function throughout treatment is required.
Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long halve-lives such as trastuzumab, may also be at risk of developing cardiotoxicity. The half-life of trastuzumab is approximately 28-38 days, and it may remain in the circulation for up to 27 stopping treatment with trastuzumab. If anthracyclines are used earlier than 27 weeks after stopping trastuzumab, careful monitoring of cardiac function is recommended.
There is a risk of marked disturbances of hematopoiesis after pretreatment with medications that affect the bone marrow (i.e. cytostatic agents, sulphonamides, chloramphenicol, diphenylhydantoin, amidopyrine derivates, antiretroviral agents).
Epirubicin is mainly metabolized by the liver. Concomitant use of medicinal products that affect hepatic function may affect the metabolism or pharmacokinetic of Epirubicin and e its efficacy and/or toxicity.
The combination of epirubicin with potentially hepatotoxic drugs may affect with the hepatic metabolism and/or biliary excretion of epirubicin lead to an increase in the toxicity of the substance. This can lead to an increase in side effects.
Concomitant use of other cytostatic drugs increases the risk of gastrointestinal side effects.
Concomitant administration of medicinal products that cause a delay of uric acid excretion (e.g. sulfonamides, certain diuretics) may lead to increased hyperuricemia.
Epirubicin binds to heparin, which can lead to precipitation and loss of action of both active substances.
Concomitant use of verapamil reduced the availability of epirubicin by increasing the clearance. This results in increased systemic availability of epirubicin metabolites. Dexverapamil may alter the pharmacokinetics of epirubicin and possibly increase its myelosuppressive effect.
Cimetidin increase the AUC of epirubicin by 50% and should be discontinued during treatment with epirubicin.
When given prior to epirubicin, paclitaxel can increase the plasma concentrations of epirubicin and its metabolites. The metabolites are neither toxic nor active, however. Administration of paclitaxel or docetaxel after epirubicin does not affect the kinetics of epirubicin.
The combination can be used if intake is delayed. Epirubicin and paclitaxel should be infused with at least a 24-hour interval between the two agents.
The use of live vaccines should be avoided in patients receiving epirubicin. Killed or inactivated vaccines may be used, however, the response to such vaccines may be demised.
One study found that docetaxel may increase the plasma concentrations of epirubicin metabolites when administered immediately after epirubicin.
The initial distribution of epirubicin from blood into tissues may be accelerated by quinine and this may have an influence on the red blood cell partitioning of epirubicin.
The coadministration of interferon α_{2b} may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin.
Increased myelosuppression may occur in patients receiving combination therapy with anthracycline and dexrazoxane.

4.6 Fertility, pregnancy and lactation

Pregnancy

Experimental data suggest that epirubicin may harm the foetus. Like most other anticancer agents, epirubicin has shown in animals mutagenic and carcinogenic properties.

Women of childbearing potential should be fully aware of the harm to the foetus in case of occurrence of pregnancy during epirubicin therapy. Epirubicin should not be used in pregnant women or women of childbearing potential unless the potential benefit to the mother outweighs the potential risk to the foetus. Women should not become pregnant during and up to 6 months after treatment.

Breastfeeding

It is not known whether Epirubicin is excreted in breast milk. Risk to the infant cannot be excluded. Therefore you have to stop breast-feeding during epirubicin treatment.

Fertility

There is no clear evidence if epirubicin influence human fertility or acts teratogen. Epirubicin may cause chromosome damage in human sperm. Men being treated with epirubicin are advised not to father a child during treatment and up to 6 months after treatment and to seek advice for sperm conservation before therapy.

Both men and women receiving epirubicin should be informed about the potential risk of adverse effects on the offspring.

Epirubicin may cause amenorrhea or premature menopause in premenopausal women.

4.7 Effects on ability to drive and use machines

No studies are available on the effects on the ability to drive or use machines. However, epirubicin can cause episodes of nausea and vomiting that can temporarily affect the ability to drive and operate machines.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with epirubicin.

The frequencies of the undesirable effects are classified as follows:

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 experience undesirable effects. The most common undesirable effects are myelosuppression, gastrointestinal effects, loss of appetite, alopecia, infection.

Infections and infestations	Very 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 (leukopenia, granulocytopenia and neutropenia, anaemia and febrile neutropenia)
	Uncommon	Thrombocytopenia
	Not known	Haemorrhage and tissue hypoxia as a result of myelosuppression
Immune system disorders	Rare	Anaphylactic / anaphylactoid reactions (including skin rash, itching, fever, chills)

	Not known	Anaphylactic shock
Metabolism and nutrition disorders	Common	Anorexia, Dehydration
	Rare	Hyperuricemia (as a result of rapid lysis of neoplastic cells [tumour lysis syndrome])
Nervous system disorders	Rare	Dizziness
Eye disorders	Not known	Conjunctivitis, keratitis
Cardiac disorders	Rare	Congestive heart failure (CHF) (dyspnoea, enema, hepatomegaly, ascites, pulmonary enema, pleural effusions, extrasystoles), 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, esophagitis, stomatitis, pain or burning sensation, gastric erosion and ulcers, bleeding in the gastrointestinal tract, abdominal pain, vomiting, diarrhoea, nausea
	Not known	Hyperpigmentation of the oral mucous membranes
Skin and subcutaneous tissue disorders	Very common	Alopecia
	Rare	Urticaria
	Not known	Local reaction, redness of skin, itch, skin changes, erythema, flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiation of the 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, Azospermia
	Not known	Premature entry of menopause in premenopausal women
General disorders and administration site conditions	Common	Redness along the infusion vein
	Rare	Malaise, asthenia, fever, chills
	Not known	Phlebosclerosis, headache, local pain, severe cellulitis, tissue necrosis after perivenous injection can cause
Investigations	Rare	Changes in transaminase levels
	Not known	Asymptomatic decrease in left ventricular ejection fraction (LVEF)

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 the national reporting system.

4.9 Overdose

Symptoms

Very high single doses of epirubicin may cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 days.

Acute overdosage can lead to toxic gastrointestinal symptoms (mainly mucositis) and acute complications of the cardiovascular system.

In case of overdose subsequent heart failure was observed up to 6 months after treatment with anthracyclines.

Therapy

In the event of intoxication, the administration of epirubicin should be discontinued immediately and symptomatic treatment initiated.

In cardiac involvement a cardiologist should be consulted.

In severe myelosuppression substitution of the missing blood components and the transport of the patient in a sterile room should be considered.

Epirubicin cannot be removed by dialysis.

No specific antidote is known.

Extravasation

Accidental perivenous injection results in local necrosis and thrombophlebitis. A burning sensation in the region of the infusion indicates a perivenous administration.

Treatment of Extravasation

In case of extravasation, the infusion or injection should be stopped immediately; the needle should initially be left to be removed after a short aspiration. It is recommended to locally apply DMSO 99% to an area twice of the area affected by extravasation (4 drops to 10 cm^2 skin surface). Repeat this procedure three times a day over a period of 14 days. Optionally, debridement should be considered. Cooling of the area, eg. for pain reduction, sequentially carried out with DMSO application (vasoconstriction vs. vasodilatation) should be considered. Other measures are controversial discussed in the literature and of indeterminate value.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cytotoxic antibiotics and related substances

ATC code: L01DB03

Epirubicin is a 4` epimer of the anthracycline antibiotic doxorubicin. The pharmacological properties are similar to those of other anthracyclines. Epirubicin is active in all phases of the cell cycle and shows maximum cytotoxic effects in the S and G2 phase of the cell cycle. The exact antineoplastic mechanism of action is not fully understood, but is most likely due to the ability to form by intercalation between DNA base pairs complexes with DNA. This results in serious disturbances in the tertiary structure of the DNA and RNA synthesis. Intercalation also seems to interfere with the topoisomerase-DNA "cleavable complex". Other mechanisms of action are discussed, the formation of free radicals, a direct membrane action and the chelation with metal ions.

Epirubicin has proven to be act on a wide spectrum of experimental tumours including L1210 and P388 leukaemia's, sarcomas SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

5.2 Pharmacokinetic properties

After intravenous administration, epirubicin is quickly distributed to the most tissues. Despite the large distribution volume, epirubicin does not cross the blood-brain barrier in measurable quantities.

Epirubicin undergoes triphasic plasma clearance characterized by a rapid initial distribution phase (t1/2α: 3.0 to 4.8 minutes), followed by an intermediate phase of elimination (t1/2β: 1.1 to 2.6 hours) and slow terminal elimination phase (t1/2γ: 18-45 hours).
The volume of distribution (Vd) of epirubicin is 32-46 l/kg.
The plasma clearance is 30-100 l/h.
Epirubicin is mainly metabolised in the liver. One active metabolite (epirubicinol) and 6 inactive metabolites (epirubicinol glucuronide, epirubicin glucuronide and 4 aglycones) could be identified.
Epirubicinol has in vitro as epirubicin a 10-fold lower cytotoxic activity. For the other metabolites no significant activity or toxicity could be detected.
Approximately 6-7% of the administered dose excreted unchanged renally, less than 5% as glucuronide and lower proportions than epirubicinol. After hepatic metabolism about 35% of the administered dose is eliminated by biliary excretion. The biliary and renal clearance are 8-33 and 4-15 l/h.

5.3 Preclinical safety data

The toxic effects after repeated administration have been studied in rats, rabbits and dogs. The most important target organs in these species are the hem lymphopoietic system, the gastrointestinal tract, the kidneys, liver and genitalia.
Epirubicin show cardiotoxic effects in rats, rabbits and dog.

Like other anthracyclines epirubicin is mutagen, genotoxic, embryotoxic and carcinogen in rats.
No birth defect have been seen in rats or rabbits, however, like other anthracyclines and cytostatic drugs, epirubicin must be regarded as potentially teratogenic
A local tolerance study in rats and mice showed extravasation of epirubicin causes necrosis.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Sodium Chloride
Water for Injections
Hydrochloric acid for pH adjustment
Water for Injection

6.2. INCOMPATIBILITIES

Epirubicin must not be mixed with heparin due to possible precipitation.
When Epirubicin HCl Karma 2mg/ml solution for injection is given in combination with other cytostatic drugs, no direct mixture of the drugs should be used.
Contact with alkaline solutions should be avoided as this can lead to hydrolysis.

6.3. SHELF LIFE

2 years

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Keep the vial in the outer carton in order to protect from light.
Store in refrigerator (2°C - 8°C).
For single use. Discard any unused content.

6.5. NATURE AND CONTENTS OF CONTAINER

Colorless glass vials (type I), with a chlorobutyl rubber stopper and flip-off cap.
One vial per box with 25 ml Solution for Injection (50mg/25ml)

6.6. Special instructions for disposal

Instructions for use and handling

The solution for injection should be checked for the absence of particles before use. Solutions with particles may not be used and must be disposed of in accordance with the requirenmnets for cytostatic drugs. For immediata use-

Epirubicin HCl Karma 2mg/ml solution for injection is a ready-to-use solution with a pH of 2.5-3.5. Epirubicin HCl Karma 2mg/ml solution for injection should be brought to room temperature prior to administration. Epirubicin HCl Karma 2mg/ml solution for injection contains no preservatives and therefore is intended for single use only.

As with other cytotoxic drugs recautions should be taken to avoid skin and mucosal contacts. When dealing with Epirubicin HCl Karma 2mg/ml solution for injection protective clothes must be worn. If Epirubicin HCl Karma 2mg/ml solution for injection comes into contact with the skin or mucous membrane, thorough washing with soap and water is recommended. Not use a brush to avoid additionally mechanically damage of the skin.

If Epirubicin HCl Karma 2mg/ml solution for injection comes into contact with the eyes, immediately rinse thoroughly with water or with soap and water or with sodium bicarbonate solution and consult a doctor.

Instructions for disposal

For single use, only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytostatic drugs.

6.7 DRUG PRODUCT SPECIFICATIONS

BP

7. REGISTRATION HOLDER / MARKETING AUTHORIZATION HOLDER

M/s Lab Diagnostic Systems (SMC) Pvt Ltd

Plot no 36-A, PSIC, SIE, Taxila, Rawalpindi

7.1. Manufacturer (As per Registration letter)

Name of Manufacturing Site Address

Marketing Authorization Holder in the exporting country: Pharma resource GmbH Domeierstrabe 29/31 31785 Hamein Germany

Manufacturer: Thymoorgan Pharmazie GmbH Schiffgraben 3 38690 Golsar – Vienenburg Germany

8. REGISTRATION / MARKETING AUTHORIZATION NUMBER

103763

9. DATE FROM WHICH MARKETING IS AUTHORIZED:

15/06/2020

10. DATE OF REVISION OF THE TEXT:

N/A