

DBL™ EPIRUBICIN HYDROCHLORIDE SOLUTION FOR INJECTION

Name of medicine

Epirubicin hydrochloride

Presentation

DBL™ Epirubicin Hydrochloride Solution for Injection is a clear red solution of epirubicin hydrochloride and sodium chloride in Water for Injections. Sodium hydroxide and hydrochloric acid are added as necessary to adjust the pH. The solution is available as a 2 mg/mL solution as 10 mg/5 mL, 20 mg/10 mL and 50 mg/25 mL presentations.

Uses

Actions

The mechanism of action of epirubicin hydrochloride has not been fully elucidated but is probably related to its ability to bind DNA. Cell culture studies have shown cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin hydrochloride has proved to be active on the following experimental tumours: L 1210 ascites and P388 leukaemias, sarcoma SA 180 (solid and ascitic forms), melanoma B 16, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38.

The specificity of epirubicin hydrochloride toxicity appears to be related primarily to proliferative activity of normal tissue. Thus, bone marrow, gastrointestinal tract, lymphoid organs and the gonads are the main normal tissues damaged. Degenerative or functional alterations in liver and kidneys were also seen in animals dosed with epirubicin hydrochloride.

Like most other antitumour and immunosuppressant agents, epirubicin hydrochloride, under experimental conditions, has mutagenic properties and is carcinogenic in laboratory animals (see **Warnings and Precautions, Use in Pregnancy**).

Toxicity studies in animals have indicated that on a weight (mg per kg) basis epirubicin hydrochloride has a better therapeutic index and less systemic and cardiac toxicity than doxorubicin.

Pharmacokinetics

In patients with normal hepatic and renal function, plasma levels after intravenous injection of 75 to 90 mg/m² of the drug follow a triexponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. Plasma levels of the drug's main metabolite, the 13-OH derivative, are constantly somewhat lower and virtually parallel to those of the unchanged drug.

Epirubicin hydrochloride is eliminated mainly through the liver; high plasma clearance values (0.9 L/min), indicate that the slow elimination of epirubicin is due to extensive tissue distribution. Urinary excretion accounts for approximately 11% of the administered dose in 48 hours. However, like doxorubicin, biliary excretion is likely to be the major excretion route. Impairment of liver function delays plasma clearance. As with doxorubicin, epirubicin hydrochloride may not be expected to cross the blood-brain barrier. When epirubicin hydrochloride is administered intravesically, the systemic absorption is minimal.

There is evidence for a dose-response and dose-toxicity relationship for epirubicin in breast cancer, and to a lesser extent for lymphoma. This relationship is steeper and therefore more evident for doses of epirubicin above 90 mg/m². Current data indicates that an increase in dose (for dose intensity) produces greater response rates.

Epirubicin hydrochloride is immunosuppressive in animals. Although there are no clinical data on the immunosuppressive effects of epirubicin hydrochloride, effects similar to those seen with doxorubicin may be expected.

Indications

Epirubicin hydrochloride has produced responses in a wide spectrum of neoplastic diseases, and is indicated for the treatment of:

- breast cancer,
- gastric cancer,
- ovarian cancer,
- small cell lung cancer,

- lymphoma (non-Hodgkin's lymphoma),
- advanced/metastatic soft tissue sarcoma, and
- Superficial bladder cancer (Tis; Ta).

In bladder cancer, epirubicin hydrochloride is also indicated in the prophylaxis of recurrence after transurethral resection of stage T1 papillary cancers and stage Ta multifocal papillary cancers (Grade 2 and 3).

Epirubicin has also shown antitumour activity in the following tumours:

- carcinoma of the oesophagus
- primary hepatocellular carcinoma
- pancreatic carcinoma
- carcinoma of the head and neck
- acute leukaemias and multiple myeloma

Dosage and administration

Dosage

DBL[®] Epirubicin Hydrochloride Solution for Injection is intended for intravenous or intravesical administration only. It must not be administered by the intramuscular, subcutaneous or oral routes. DBL[®] Epirubicin Hydrochloride Solution for Injection is for use in one patient on one occasion only. Discard any residue.

Care in the intravenous administration of DBL[®] Epirubicin Hydrochloride Solution for Injection will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions, such as urticaria and erythematous streaking (see **Warnings and Precautions**).

NOTE: The recommended lifetime cumulative dose limit is 900 mg epirubicin hydrochloride/m² body surface area.

Under conditions of normal recovery from drug-induced toxicity (particularly bone marrow depression and stomatitis), the recommended dosage schedule in adults, as described below, is as a single intravenous injection administered at 21 day intervals.

Standard doses are 75 to 90 mg/m². Epirubicin hydrochloride produces predominantly haematological dose-limiting toxicities which are predicted from the known dose-response profile of the drug. Based on the patient's haematological status the physician should determine the choice of dose.

Higher doses, up to 135 mg/m² as a single agent and 120 mg/m² in combination, every 3-4 weeks have been effective in the treatment of breast cancer. In the adjuvant treatment of early breast cancer patients with positive lymph nodes, doses ranging from 100 mg/m² to 120 mg/m² every 3-4 weeks are recommended. Careful monitoring in regards to increased myelosuppression, nausea, vomiting and mucositis are recommended in this high dose setting. Consideration should be given to the administration of lower starting doses (not exceeding 75 to 90 mg/m²) for heavily pretreated patients, patients with pre-existing bone marrow depression or in the presence of neoplastic bone marrow infiltration. If epirubicin hydrochloride is used in combination with other cytotoxic drugs with potentially overlapping toxicities, the recommended dose per cycle should be reduced accordingly.

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

Small cell lung cancer (previously untreated): 120 mg/m² day 1, every three weeks.

Non-small cell lung cancer (squamous large cell and adeno-carcinoma, previously untreated): 135 mg/m² day 1 or 45 mg/m² days 1, 2, 3, every three weeks.

While no specific dose recommendation can be made 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).

Intravesical Administration

For the treatment of papillary transitional cell carcinoma of the bladder, a therapy of 8 weekly instillations of 50 mg (in 25 to 50 mL of saline solution) is recommended.

In the case of local toxicity (chemical cystitis) a dose reduction up to 30 mg is advised. For carcinoma *in situ*, depending on the individual tolerability of the patient, the dose may be increased up to 80 mg.

For prophylaxis of recurrences after transurethral resection of superficial tumours, 4 weekly administrations of 50 mg followed by 11 monthly instillations at the same dosage are recommended.

Generally, the instillate should be retained in the bladder for one hour and during instillation the pelvis of the patient should be rotated to ensure the most extensive contact of the solution with the vesical mucosa. To avoid undue dilution with the urine, the patient should be instructed not to drink any fluid in the twelve hours prior to instillation.

Intravesical administration is not suitable for the treatment of invasive tumours which have penetrated the muscular layer of the bladder wall.

Dose Modifications

Impaired hepatic function: As clinical toxicity may be increased by the presence of impaired liver function, epirubicin hydrochloride dosage must be reduced if hepatic function is impaired, according to the following table:

| Serum Bilirubin Levels | Recommended Dose |
|------------------------|------------------|
| 20 - 50 micromol/L | ½ normal dose |
| Over 50 micromol/L | ¼ normal dose |

Severe renal impairment: Dosage reduction should be considered for severe renal impairment.

Haematological toxicity: Dosage reduction, delay or suspension of therapy with epirubicin hydrochloride may be necessary.

Concurrent antineoplastic agents: Lower doses may be necessary if DBL[®] Epirubicin Hydrochloride Solution for Injection is used concurrently with other antineoplastic agents.

Pharmaceutical Precautions

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 DBL[™] Epirubicin Hydrochloride Solution for Injection should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow containment system). The work surface should be protected by disposable plastic backed absorbent paper.
- All items used for administration of cleaning, including gloves, should be placed in high-risk, waste-disposal bags for high temperature incineration.
- 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.
- Accidental contact with the eyes or skin should be treated immediately. Copious lavage with water is appropriate treatment for contact with the eyes, whereas water or soap and water, or sodium bicarbonate solution may be used on the skin; medical attention should be sought.

Administration

The product does not contain a preservative. Use once only and discard any residue.

Intravenous Administration

It is recommended that DBL[™] Epirubicin Hydrochloride Solution for Injection be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection USP or 5% Glucose Injection USP. The tubing should be attached to a Butterfly needle inserted preferably into a large vein. The rate of administration is dependent on the size of the vein and the dosage. However, the dosage should be administered between 3 to 20 minutes to minimise the risk of thrombosis and perivenous extravasation.

A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein (see **Warnings and Precautions**).

Intravesical Administration

DBL™ Epirubicin Hydrochloride Solution for Injection, is 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. During instillation, the pelvis of the patient should be rotated to ensure extensive contact of the solution with the vesical mucosa.

Compatibility

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

DBL™ Epirubicin Hydrochloride Solution for Injection is compatible with the following infusion media:

- 0.9% Sodium Chloride
- 5% Glucose
- 0.9% Sodium Chloride with 5% Glucose

DBL™ Epirubicin Hydrochloride Solution for Injection can be used in combination with other antitumour agents, but it is not recommended that it be mixed with these drugs in the same container.

DBL™ Epirubicin Hydrochloride Solution for Injection should not be mixed with heparin as these drugs are incompatible. Until specific compatibility data are available, it is not recommended that DBL™ Epirubicin Hydrochloride Solution for Injection be mixed with other drugs.

Contraindications

Situations in which patients should not be treated with intravenous epirubicin hydrochloride are:

- persisting myelosuppression or severe stomatitis induced by previous drug therapy or radiotherapy,
- presence of generalised infections,
- marked liver function impairment,
- previous history of, or in the presence of, cardiac impairment (severe arrhythmias and myocardial insufficiency, previous myocardial infarction),
- previous treatments with maximum cumulative doses of mitozantrone, mitomycin C or other anthracyclines, such as doxorubicin or daunorubicin,
- hypersensitivity to epirubicin, other anthracyclines or anthracenediones,
- pregnancy and lactation.

Contraindications for intravesical use are:

- invasive tumours that have penetrated the bladder wall,
- urinary infections,
- inflammation of the bladder,
- catheterisation problems.
- haematuria

Warnings and precautions

Epirubicin hydrochloride should be administered only under the supervision of qualified physicians experienced in 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 hydrochloride.

While treatment with high doses of the drug (eg. Greater than or equal to 90 mg/m² every three to four weeks) causes adverse events generally similar to those seen in standard doses (eg. < 90 mg/m² every three to four weeks), the severity of neutropenia and stomatitis/mucositis may be increased. In particular, treatment with high doses of the drug requires special attention for possible clinical complications due to profound myelosuppression. However, high doses of epirubicin have been administered to a large

number of untreated patients (either for their advanced disease or in the adjuvant setting) and have caused adverse events which are no different from those seen at conventional doses except for the degree (severity) of the reversible neutropenia (< 500 neutrophils/L) which occurred in the majority of patients. Only a few of these patients have required hospitalisation for severe infectious complications.

Initial treatment with epirubicin hydrochloride requires close observation of the patient and extensive laboratory monitoring including assessment of cardiac function. During each cycle of treatment patients must be carefully and frequently monitored. A blood count, renal and liver function tests should be carried out prior to each epirubicin hydrochloride treatment. The routine assessment of cardiac function may include electrocardiogram (ECG) and the evaluation of left ventricular ejection fraction (LVEF).

EPIRUBICIN HYDROCHLORIDE MUST BE HANDLED WITH CARE. IF THE PREPARATION COMES IN CONTACT WITH THE SKIN OR MUCOSAE, THE APPROPRIATE AREAS SHOULD BE WASHED IMMEDIATELY AND THOROUGHLY WITH SOAP AND WATER OR SODIUM BICARBONATE SOLUTION.

Epirubicin hydrochloride is intended for use under the direction of those experienced in cytotoxic therapy. The rate of administration is dependent on the size of the vein and the dosage. It is important that the dose be administered in not less than 3 to 4 minutes. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Severe local tissue necrosis will occur if there is extravasation during administration. Venous sclerosis may result from infection into a small vessel or from repeated injections into the same vein. Epirubicin hydrochloride must not be given by the intramuscular or subcutaneous route.

Epirubicin hydrochloride is not an antimicrobial agent.

Haematological Considerations

Haematological monitoring should be undertaken regularly in view of the possibility of severe bone marrow depression which may occur. Leucopenia is usually transient with the recommended dosage schedules, reaching a nadir between 10 and 14 days after administration. A return to normal blood values usually occurs within 21 days from administration. However, leucopenia requires careful haematologic monitoring, since a persistent severe myelosuppression may result in super-infections and/or haemorrhages, which may require intensive care.

Secondary acute myelogenous leukaemia, with or without a pre-leukaemic phase, had been reported in patients treated with topoisomerase II inhibitors, including anthracyclines such as epirubicin (see **Adverse Effects**).

Anthracycline-Induced Cardiotoxicity

Patients receiving epirubicin hydrochloride should be monitored for anthracycline-induced cardiotoxicity.

Heart function should be carefully monitored during treatment in order to minimise the risk of cardiac failure, of the type described for other anthracycline compounds. Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin hydrochloride or within two to three months post treatment. Cardiomyopathy induced by anthracyclines is associated with persistent QRS voltage reduction, prolongation beyond normal limits of the systolic time interval (PEP/LVET) and a reduction of the ejection fraction 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 increases rapidly with increasing total cumulative doses of the drug in excess of 900 mg/m²; this cumulative dose should only be exceeded with extreme caution.

The onset of cardiac failure may be sudden and early recognition may increase the likelihood of benefit from treatment. Heart failure has been reported even several weeks to several months after discontinuing treatment and the risk may be higher in patients with active or dormant cardiovascular disease, concomitant or previous radiation of the mediastinal-pericardial area, hypertensive cardiomyopathy, previous therapy with other anthracyclines/anthracenediones concomitant use of other drugs with the ability to suppress cardiac contractility or treatment with other potentially cardiotoxic agents such as high dose cyclophosphamide or 5-fluorouracil or trastuzumab. 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 where possible. If anthracyclines are used before this time careful monitoring of cardiac function is recommended.

In such patients a reduction of the total cumulative dose may be required and the monitoring of cardiac function must be particularly strict. The risk-benefit of continuing epirubicin hydrochloride treatment under conditions of impaired cardiac function has to be carefully evaluated. However cardiotoxicity with epirubicin hydrochloride may occur in lower cumulative doses whether or not cardiac risk factors are present. It is probable that the toxicity of epirubicin hydrochloride and other anthracyclines or anthracenediones is additive.

The total (cumulative) dose levels of epirubicin hydrochloride do correlate with the incidence of drug-induced congestive cardiac failure (cardiomyopathy). At a cellular level the nature of epirubicin hydrochloride-induced cardiac toxicity appears to be similar to that of doxorubicin. Limitation of the total lifetime dose of epirubicin hydrochloride to 900 mg/m² in good risk patients reduces the likelihood of drug-induced cardiomyopathy.

It is suggested that an ECG be taken before treatment. Alterations of the ECG, such as flattening or inversion of the T wave, depression of the S-T segment, or the onset of arrhythmias, are generally transient and reversible and need not necessarily indicate that treatment should be stopped.

It is also advisable to assess cardiac function by other techniques, such as echocardiography and measurement of the ejection fraction by radionuclide angiography. The technique should be consistent throughout.

Impaired Hepatic Function

As toxicity of epirubicin hydrochloride is enhanced by impaired liver function or bile outflow, the major route of elimination being the hepatobiliary system, dosages should be reduced in patients with impaired hepatic function (see also **Dosage and Administration**). Serum total bilirubin and AST levels should be evaluated before and during treatment with epirubicin hydrochloride. Patients with severe hepatic impairment should not receive epirubicin hydrochloride.

Impaired Renal Function

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin hydrochloride excreted by this route.

Patients with severe renal impairment (serum creatinine concentration exceeding 5 mg/dL) may require dosage reductions. The drug has not been studied in those undergoing dialysis.

Immunosuppression 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. 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.

Other

Epirubicin hydrochloride may enhance radiation-induced toxicity such as skin reactions and mucositis and may potentiate the toxicity of other anticancer therapies. This has to be taken into account particularly when using the drug in high doses and the availability of supportive care and facilities has to be considered before initiating high dose-intensive regimens.

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 hydrochloride

Like other cytotoxic drugs, epirubicin hydrochloride may induce hyperuricaemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

Epirubicin may impart a red colour to the urine for one to two days after administration. Patients should be advised that such an event is not a cause for alarm.

Secondary acute myelogenous leukaemia (AML) has been reported in patients treated with anthracyclines; risk of refractory AML increases when epirubicin is combined with other DNA-damaging antineoplastics, when patients have had extensive exposure to cytotoxic drugs, or when anthracycline doses have been escalated. The cumulative risk for adjuvant epirubicin therapy-related leukaemia is estimated as 0.2% and 0.8% at 3 and 5 years respectively.

Pregnancy and Lactation**Use in Pregnancy (Category D¹)**

There is no specific information available at present concerning the use of epirubicin hydrochloride in human pregnancy. As a general rule, it is advisable that DBL™ Epirubicin Hydrochloride Solution for Injection not be administered to patients who are pregnant and women of child-bearing potential who have to undergo epirubicin therapy should be appraised of the potential hazard to the foetus and should be advised to avoid becoming pregnant during treatment. Given the mutagenic potential of epirubicin, the medicine could induce chromosomal damage in human spermatozoa and males undergoing epirubicin treatment should employ contraceptive measures. However, as it has been shown to be embryotoxic and fetotoxic in animals, it should not be used in patients who are pregnant or are likely to become pregnant.

Use in Lactation

It is likely that epirubicin hydrochloride is excreted in breast milk, therefore it is not recommended for nursing mothers unless the expected benefits outweighs any potential risk.

Effects on ability to drive and use machines

Epirubicin is likely to produce severe adverse effects or presumed to be potentially dangerous, which may impair the patient's ability to concentrate and react and therefore constitute a risk in the ability to drive and use machines.

Other**Carcinogenicity, Mutagenicity, Impairment of Fertility:**

Although no studies have been conducted with epirubicin hydrochloride, it may be expected, like doxorubicin, to cause infertility during the period of drug administration. In women, epirubicin hydrochloride may cause amenorrhoea. After termination of therapy, ovulation and menstruation may be expected to return in a few months, often accompanied by normal fertility. Premature menopause may occur.

In male patients, oligospermia or azospermia may be permanent, although fertility may return several years after ceasing therapy. Given the mutagenic potential of epirubicin hydrochloride, the drug could

¹ *Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.*

induce chromosomal damage in human spermatozoa; therefore, males undergoing epirubicin hydrochloride treatment should employ contraceptive measures.

Epirubicin is mutagenic, clastogenic, and carcinogenic in animals.

Adverse effects

Dose-limiting toxicities are myelosuppression and cardiotoxicity (described in detail under **Warnings and Precautions**).

Adverse effects observed are:

More Common Reactions (>5%)

Haematological: Myelosuppression, leucopenia, neutropenia, thrombocytopenia, mild anaemia, secondary infection.

Cardiovascular: Transient ECG changes, including low QRS voltage, tachycardia, arrhythmias, T wave flattening, ST depression and T inversion.

Gastrointestinal: Nausea, vomiting, diarrhoea and mucositis (erythema, erosions/ulcerations, bleeding). Mucositis may appear 5 to 10 days after the start of treatment and usually involves stomatitis with areas of painful erosions, mainly along the sides of the tongue and on the sublingual mucosa.

Dermatological: Alopecia, including the interruption of beard growth, usually reversible, occurs in 60 to 90% of treated cases.

Application Site: Erythematous streaking along the infused vein.

General: Dehydration.

Less Common Reactions (<5%)

Haematological: Severe thrombocytopenia, anaemia, severe myelosuppression, pancytopenia, sepsis, septicemia, septic shock, tissue hypoxia, haemorrhage and death.

Cardiovascular: Cardiomyopathy, congestive heart failure, cardiomegaly, atrioventricular and bundle branch block, tachyarrhythmias (premature ventricular contractions, ventricular tachycardia, bradycardia), asymptomatic drops in left ventricular ejection fraction..

Gastrointestinal: Oesophagitis, bleeding, hyperpigmentation of oral mucosa and abdominal pain or burning sensation.

Dermatological: Local toxicity, rash/itch, transient urticaria, flushes, skin and nail hyperpigmentation, photosensitivity and hypersensitivity of irradiated skin.

Application Site: Vesication, phlebitis, thrombophlebitis and venous sclerosis. Local pain, severe cellulitis and skin necrosis following perivenous drug extravasation.

Ocular: Conjunctivitis, keratitis.

Hepatic: Changes in transaminase levels.

General: Chills, shock, fever, anorexia, amenorrhoea, azoospermia, malaise/asthenia, hot flushes. Anaphylaxis may occur.

CNS: Weakness, dizziness, confusion, depression, paraesthesia.

Hyperuricaemia may occur as a consequence of the extensive purine catabolism which accompanies drug-induced rapid cell kill of highly chemosensitive neoplasms (tumour lysis syndrome). Hydration, urine

alkalinisation and allopurinol administration will help to prevent or minimise the adverse effects of hyperuricaemia.

Intravesicular administration: As drug absorption is minimal, systemic side effects are rare; more frequently chemical cystitis, sometimes haemorrhagic, and bladder constriction has been observed. Dose reduction (40%) may be necessary in these cases.

Serious or Life-threatening Reactions

Myelosuppression: This accompanies effective epirubicin hydrochloride treatment in almost 100% of patients and represents the acute dose-limiting toxicity of this drug. Leucopenia is the predominant effect with thrombocytopenia and anaemia occurring less frequently. Leucopenia is usually more severe after administration of high-dose regimens. Under these conditions appropriate bone marrow support (eg. peripheral blood progenitor cells and/or colony-stimulating factors) may be required. Intravenous antibiotics should be given in the presence of febrile neutropenia.

Myelosuppression is more common in patients who have had extensive radiotherapy, bone marrow infiltration by tumour or impaired liver function (when appropriate dosage reduction has not been adopted) (see **Dosage and Administration**).

Other Haematological: The occurrence of secondary acute myelogenous leukaemia, with or without a pre-leukaemic phase, has been reported in patients treated with topoisomerase II inhibitors, including anthracyclines such as epirubicin. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, or when patients have been heavily pretreated with cytotoxic drugs or when doses have been escalated. This complication has been reported in 1 to 2% of patients receiving epirubicin-containing combination chemotherapy as adjuvant therapy in breast cancer. These leukaemias can have a short (1 to 3 year) latency period.

Mucositis: This is frequent and painful and most commonly develops 5 to 10 days after treatment. It typically begins as a burning sensation in the mouth and pharynx. The mucositis may involve the vagina, rectum and oesophagus, and progress to ulceration with a risk of secondary infection. Nausea and vomiting may be prevented or alleviated by the administration of appropriate anti-emetic therapy. The mucositis usually subsides in 10 days.

Cardiotoxicity: The cardiac abnormalities caused by treatment can be separated into 2 categories:

ECG alterations, and

Congestive heart failure (CHF)

ECG changes following epirubicin hydrochloride treatment occur in about 10% of patients. The changes are usually reversible and do not appear to be related to the subsequent development of congestive cardiac failure.

Epirubicin, like other members of this class of drugs, may cause congestive cardiac failure (cardiomyopathy). This effect is cumulative dose-dependent and represents the cumulative dose-limiting toxicity of the drug. The following measures may identify patients with early anthracycline cardiomyopathy: progressive flattening or inversion of the T waves (mainly in the left precordial leads), low QRS voltage, prolonged systolic time interval, reduced ejection fraction (echocardiography or by cardiac gated pool scanning) or cardiac biopsy showing characteristic electromicroscopic changes. Early diagnosis and management may control the heart failure. Epirubicin hydrochloride-induced cardiomyopathy can be fatal (see **Warnings and Precautions**). Delayed cardiac toxicity is represented by a characteristic cardiomyopathy which clinically is manifested by symptoms/signs of ventricular dysfunction/CHF (such as dyspnoea, pulmonary oedema, dependent oedema, hepatomegaly, ascites, pleural effusion, gallop rhythm).

Delayed cardiotoxicity mainly develops during the course of therapy with epirubicin and up to two to three months afterwards, but late events (several months to years after treatment termination) have occurred. Pericardial effusion has also been described.

Direct administration of epirubicin (or epirubicin-containing regimens) and lipiodol into the hepatic artery ('transcatheter arterial embolisation', or TAE) for the loco-regional therapy of primary hepatocellular

carcinoma (PHCC) or liver metastases has been reported to produce gastro-duodenal ulcers, probably due to reflux of the drugs into the gastric artery, and narrowing of bile ducts ('biloma') due to drug-induced sclerosing cholangitis.

Interactions

Epirubicin hydrochloride is mainly used in combination with other cytotoxic drugs and additive toxicity may occur especially with regard to bone marrow/haematologic and gastrointestinal effects. In addition, the concomitant use of epirubicin hydrochloride with other antitumour drugs which have been reported as potentially cardiotoxic (eg. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes, trastuzumab), as well as the concomitant use of other cardioactive compounds (eg. calcium channel blockers), required a close monitoring of cardiac function throughout treatment.

Concurrent mediastinal radiotherapy and epirubicin hydrochloride may be associated with enhanced myocardial toxicity of epirubicin hydrochloride.

Epirubicin hydrochloride is extensively metabolised by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicin hydrochloride metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

Cardiotoxic drugs: Concurrent administration of epirubicin hydrochloride and cardiotoxic drugs such as propranolol and calcium channel blockers may precipitate CHF.

Propranolol: concurrent administration of epirubicin and propranolol may result in an additive cardiotoxic effect.

Cimetidine: increased the AUC of epirubicin hydrochloride by 50% and should be stopped during treatment with epirubicin hydrochloride.

When given prior to epirubicin, paclitaxel can cause increase plasma concentrations of unchanged epirubicin. Co-administration of paclitaxel or docetaxel did not effect the pharmacokinetics of epirubicin, when epirubicin was administered prior to the taxane.

Live Vaccines: The use of live attenuated vaccines in the presence of immunosuppression may increase the risk and severity of infection in response to the vaccine. Such vaccinations should only be administered with due regard for these theoretical risks.

Effects on Laboratory Tests

Not known.

Overdosage

A 36 year old man with non-Hodgkin's lymphoma received daily epirubicin injection 95 mg/m² for five consecutive days. Five days later, he developed bone marrow aplasia, grade 4 mucositis and gastrointestinal bleeding. No signs of acute cardiac toxicity were observed. He was treated with antibiotics, colony stimulating factors and antifungal agents and recovered completely. A 63 year old woman with breast cancer and liver metastasis received a single dose of epirubicin 320 mg/m², which resulted in hyperthermia, multiple organ failure (respiratory and renal), lactic acidosis, increased lactate dehydrogenase and anuria, and death within 24 hours of administration.

Additional instances of administration of doses higher than recommended have been reported at doses ranging from 150 to 250 mg/m². The observed adverse events in these patients were qualitatively similar to known toxicities of epirubicin. Most of the patients recovered with appropriate supportive care.

Very high single doses of epirubicin hydrochloride may be expected to cause acute myocardial degeneration within 24 hours, and severe myelosuppression (mainly leucopenia and thrombocytopenia) within 10 to 14 days and gastrointestinal toxic effects (mainly mucositis).

Treatment should aim to support the patients during this period and should utilise measures such as reverse barrier nursing. If an overdose occurs, supporting treatment (including antibiotic therapy, blood

and platelet transfusions, colony stimulating factors and intensive case as needed) should be provided until the recovery from toxicities. Delayed cardiac failure may occur up to 6 months after the overdose. Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines.

In case of overdose, immediately contact the Poisons Information Centre for advice. (In Australia, call 13 11 26; in New Zealand call 0800 764 766.)

Pharmaceutical precautions

Special Precautions for Storage

DBL™ Epirubicin Hydrochloride Solution for Injection should be stored from 2 to 8°C. Refrigerate, do not freeze. Protect from light.

Medicine classification

Prescription Medicine.

Package quantities

DBL™ Epirubicin Hydrochloride Solution for Injection is supplied in vials containing 2 mg/mL epirubicin hydrochloride, in a ready-to-use solution as shown below. The excipients are sodium chloride, water for injections.

Epirubicin Hydrochloride Solution for Injection

DBL™ Epirubicin Hydrochloride Solution for Injection 10 mg/5 mL vials

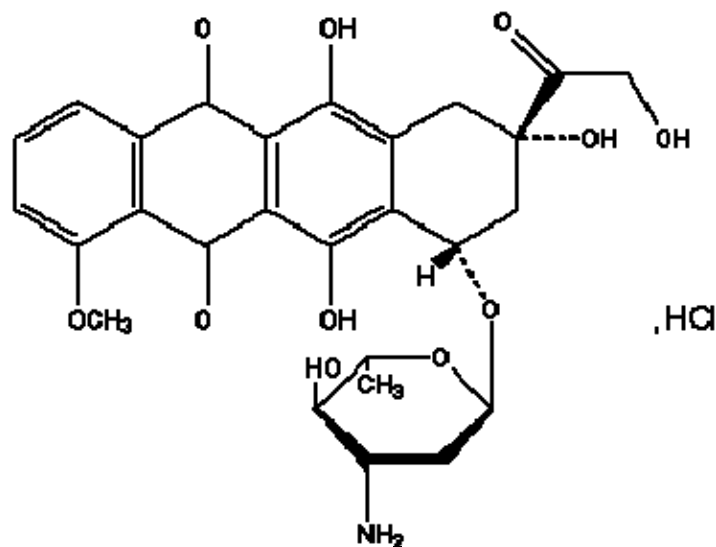
DBL™ Epirubicin Hydrochloride Solution for Injection 20 mg/10 mL vials

DBL™ Epirubicin Hydrochloride Solution for Injection 50 mg/25 mL vials

Further information

The chemical name of epirubicin hydrochloride is (8S, 10S)-10-(3-amino-2,3,6-trideoxy-(-L-arabino-hexopyranosyloxy)-8-glycolloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxynaphthacene-5,12-dione hydrochloride. Structurally, epirubicin hydrochloride differs from doxorubicin hydrochloride only in the orientation of the hydroxyl group at the 4 position on the aminoglycoside ring.

Epirubicin hydrochloride is a red-orange, almost odourless, hygroscopic powder, sparingly soluble in water and dilute alcohol. The structure is as follows:



Molecular formula: $C_{27}H_{30}ClNO_{11}$

Relative Molecular Mass: 579.99

CAS Number: 56390-09-1

Clinical Trials

Early Breast Cancer

Data from 2 multicentre, randomised phase 3 studies support the use of epirubicin hydrochloride 100 to 120 mg/m² for the adjuvant treatment of patients with axillary-node-positive breast cancer and no evidence of distant metastatic disease (Stage II or III). In one study, an intensive cyclophosphamide/epirubicin/fluorouracil (CEF-120) regimen (epirubicin hydrochloride given in a dose of 60 mg/m² on days 1 and 8) was compared with a conventional cyclophosphamide/methotrexate/fluorouracil (CMF) regimen. A total of 716 patients were randomised, 356 to CEF and 360 to CMF. Both disease free survival and overall survival were significantly prolonged in the CEF arm at five years. Disease free survival was 62% for CEF versus 53% for CMF (p=0.01) and overall survival was 77% for CEF versus 70% for CMF (p=0.043).

In the second study, 301 patients were randomised to receive tamoxifen 20 mg/day alone for 4 years and 303 patients were randomised to receive tamoxifen for 4 years in combination with epirubicin hydrochloride 50 mg/m² on days 1 and 8 every 4 weeks for 6 cycles. Although there was no significant difference between the two arms with regard to disease free survival and overall survival, there was a trend in favour of the combined use of epirubicin hydrochloride and tamoxifen. Disease free survival at two years was 85.1% versus 77.9%, and at five years was 78.8% versus 72.9%.

Advanced Breast Cancer

Data from 4 open-label, multicentre, phase 3 studies support the use of epirubicin hydrochloride for the treatment of patients with locally advanced or metastatic breast cancer. In Study 1, an intensified cyclophosphamide/epirubicin hydrochloride/fluorouracil (CEF-100) regimen (epirubicin hydrochloride given in a dose of 50 mg/m² on days 1 and 8) was compared with a conventional CMF regimen (n=461). Studies 2 and 3 compared cyclophosphamide/epirubicin hydrochloride/fluorouracil regimens where only the dose of epirubicin hydrochloride varied. In both of these, epirubicin hydrochloride was given in a dose 50 mg/m² on day 1 and compared with either 100 mg/m² on day 1 (n=456) or 50 mg/m² on days 1 and 8 (n=164). High dose epirubicin hydrochloride (135 mg/m²) was compared to conventional dose epirubicin hydrochloride (75 mg/m²) in Study 4 (n=151).

The efficacy endpoints included response rate (RR), duration of response (DR), time to tumour progression (TTP), time to treatment failure (TTF), and overall survival (OS). In Study 1, the CEF-100 regimen produced a significantly higher RR, a significantly longer TTP and a significantly longer TTF than the CMF regimen. In studies 2, 3 and 4, the higher dose epirubicin hydrochloride containing regimens produced a significantly greater RR than the lower dose epirubicin hydrochloride containing regimens. DR and TTF were also significantly longer in Study 3 and TTP was significantly longer in Study 4 for the higher dose epirubicin hydrochloride regimens.

Name and Address of the Sponsor

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