1. TRADE NAME OF THE MEDICINAL PRODUCT

Epirubicin "Ebewe"

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2mg/ml Epirubicin hydrochloride

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion and solution for injection for intravenous use.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Malignant neoplastic diseases:
Epirubicin has shown efficacy in breast cancer.
There is some evidence that indicate objective response in non-Hodgkin's lymphoma, breast-, ovarian-, gastric-, lungcancer and leukemias.
Intravesical administration of Epirubicin has been shown to be beneficial in superficial bladder cancer.

4.2. Posology and Method of Administration

Epirubicin is not active when given orally and should not be injected intramuscularly or intrathecally.
It is advisable to give the drug via the tubing of a freely-running i.v. saline infusion after checking that the needle is well placed in the vein. This method minimises the risk of drug extravasation and makes sure that the vein is flushed with saline after the administration of the drug. Extravasation of epirubicin from the vein during injection may give rise to severe tissue lesions, even necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein. Infusion preparations are to be prepared either with 0.9 % sodium chloride or with 5% glucose.
The dose level used in most studies: When Epirubicin "Ebewe" is used as a single agent, the recommended dosage in adults is 60–90mg/m² body area; the drug should be injected i.v. over 3–5 minutes and depending on the patient's haematomedullary status, the dose should be repeated at 21-day intervals.
Meanwhile epirubicin is preferentially given in combination with other cytotoxic drugs. In these cases the dose of epirubicin should be adjusted to the toxicity of the other combination partners. A diminished dose of epirubicin of 60–75 mg/m² (or 105–120mg/m² in dose intensified regimens) is generally given in combination regimens.
When the drug is used in combination with other anti-tumour agents, the doses need to be adequately reduced. Since the major route of elimination of Epirubicin is the hepatobiliary system, the dosage should be reduced in patients with impaired liver function, in order to avoid an increase of overall toxicity. Moderate liver impairment (bilirubin: 1.4–3mg/100ml) requires a 50% reduction of dose, while severe impairment > 3mg/100 ml) necessitates a dose reduction of 75%.
Intravesical administration: As a guide 50 mg/50 ml Epirubicin diluted with saline or distilled sterile water. The solution should be retained intravesically for one hour. In case of local toxicity (chemical cystitis) a dose reduction is advised (30 mg/50 ml).

4.3. Contra-indications

Epirubicin "Ebewe" is contra-indicated in patients with hypersensitivity to the active substance and with marked myelosuppression induced by previous treatment with other antitumour agents or by radiotherapy and in patients already treated with maximal cumulative doses of other anthracyclines such as doxorubicin or daunorubicin. The drug is contra-indicated in patients with severe mucositis and in patients with a current or previous history of cardiac impairment (cardiac failure grade IV).

4.4. Special Warnings and Precautions for Use

Epirubicin "Ebewe" should be administered only under the supervision of a qualified physician experienced in antiblastic and cytotoxic therapy.
Treatment with high dose epirubicin in particular requires the availability of facilities for the care of patients with possible clinical complications due to myelosuppression.
Simultaneous use of radiation should be avoided.
Initial treatment calls for careful baseline monitoring of various laboratory parameters and cardiac function.
During each cycle of treatment with Epirubicin "Ebewe", patients must be carefully and frequently monitored. Red and white blood cells, neutrophils and platelet counts should be carefully assessed both before and during each cycle of therapy. Leukopenia and neutropenia are usually transient both with conventional and high doses, reaching a nadir between the 10th and 14th day and returning to normal values by the 21st day: they are more severe with high dose schedules. Very few patients, even receiving high doses, experience thrombocytopenia (<100,000 platelets/mm³).
Before starting therapy and if possible during treatment liver function should be evaluated (AST, ALT, alkaline phosphatase, bilirubin). A cumulative dose of 900–1000mg/m² should not be exceeded. Above this level the risk of irreversible congestive cardiac failure increases greatly. There is objective evidence that cardiac toxicity may rarely occur below this range. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart failure of the type described for other anthracyclines.
Heart failure can appear even several weeks after discontinuing treatment and may prove unresponsive to specific medical treatment. The potential risk of cardiotoxicity may increase in patients who have received concomitant, or prior, radiotherapy to the mediastinal pericardial area.
In establishing the maximal cumulative doses of epirubicin any concomitant therapy with potentially cardiotoxic drugs should be taken into account.
It is recommended that an ECG before and after treatment cycle should be carried out. Alterations in the ECG tracing, such as flattening or inversion of the T wave, depression of the S-T segment, or the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment.
Cardiomyopathy induced by anthracyclines is associated with a persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the ejection fraction. Cardiac monitoring of patients receiving Epirubicin "Ebewe" treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques such as ECG, echocardiography and, if necessary, measurement of ejection fraction by radionuclide angiography.
Like other cytotoxic agents, epirubicin may induce hyperuricemia as a result of rapid lysis of neoplastic cells. Blood uric acid levels should therefore be carefully checked so that this phenomenon may be controlled pharmacologically.
Epirubicin "Ebewe" may impart a red colour to the urine for 1–2 days after administration.

4.5. Interactions with other Medicaments and other forms of Interaction

Epirubicin should not be mixed with other drugs. But Epirubicin can be used in combination with other anti-cancer drugs.
Cimetidine increases the formation of the active metabolite of ebirubicin and the exposure of the unchanged epirubicin by pharmacokinetic interaction.
Epirubicin must not be diluted in alcaline infusion solutions (e.g. hydrogencarbonate-solutions).

4.6. Pregnancy and Lactation

There is no conclusive information as to whether epirubicin may adversely affect human fertility or cause teratogenesis. Experimental data, however, suggest that epirubicin may harm the foetus. Like most other anticancer agents, epirubicin has shown mutagenic and carcinogenic properties in animals. This product should not normally be administered to patients who are pregnant or to mothers who are breast-feeding. Women of child-bearing age should take contraceptives to prevent conception and/or reproduction during and for at least 6 months after treatment with epirubicin.

4.7. Effects on Ability to Drive and Use Machines

There have been no reports of particular adverse events relating to effects on ability to drive and to use machines.

4.8. Undesirable Effects

Apart from myelosuppression and cardiotoxicity (described under Precautions) the following adverse reactions have been described).
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 has caused adverse events which are no different from those seen at conventional doses with the exception of reversible severe neutropenia (<500 neutrophils/mm³ for <7 days) which occurred in the majority of patients. Only a few patients have required hospitalisation and supportive therapy for severe infectious complications at high doses.
very common > 10 %
Myelosuppression, Granulocytopenia, Leucocytopenia,Thrombocytopenia, Neutropenia
common > 1 %
Anaemia, hemorhagia,
rare

The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported rarely in patients concurrently treated with epirubicin in association with DNA-damaging antineoplastic agents. Such cases should have a short (1–3 year) latency period.

Immune system disorders:

Rare

As a sequel of myelosuppression, fever, infections, pneumonia, sepsis, septic shock, haemorrhages, tissue hypoxia may occur and may even lead to death. Fever, sepsis, infections hyperpyrexia, chills and urticaria have been rarely reported; anaphylaxis may occur.

Labyrinth disorders:

very common > 10 %

Nausea

Cardiac disorders:

common >1%

Cardiotoxicity

Gastrointestinal disorders:

very common > 10 %

mucositis may appear 5–10 days after the start of treatment and usually involves stomatitis with areas of painful erosions, mainly along the side of the tongue and on the sublingual mucosa

common > 1 %

nausea, vomiting and diarrhoea

Skin disorders:

very common > 10 %

alopecia, normally reversible, appears in 60–90% of treated cases; it is accompanied by lack of beard growth in males.

uncommon > 0.1%

hypersensitivity of the skin to light

pigmentation of the skin

urticaria uncommon

During intravesical administration, as drug absorption is minimal, systemic side effects are rare; more frequently chemical cystitis, sometimes haemorrhagic, has been observed.

4.9. Overdose

Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10–14 days. Treatment should aim to support the patient during this period and should utilise such measures as blood transfusions and reverse barrier nursing. Delayed cardiac failure has been seen with the anthracyclines up to 6 months after the overdosage. Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

ATC Code: L01D B 03

In vitro studies showed that epirubicin possesses cytotoxicity at least equivalent to that of doxorubicin against a variety of animal and human tumour cell lines including those derived from breast, liver, lung, gastric, colorectal, squamous cell, cervical, bladder, ovarian carcinomas, neuroblastoma and leukaemia.

The mechanism of antitumour action for epirubicin has not been completely elucidated; however, anthracyclines appear to form a complex with DNA by intercalation between the DNA strands, thus inhibiting replication and transcription. This action may be attributed, at least in part, to interference with topoisomerase-DNA 'cleavable complex' and helicase activity by anthracyclines. Reduction to semiquinone free radicals may cause damage to DNA, cell membrane lipids and mitochondria.

5.2. Pharmacokinetic Properties

Following rapid intravenous administration, epirubicin undergoes triphasic plasma elimination. Epirubicin exhibits a rapid initial (α) distribution phase ($t_{½\alpha}$ = 1.8 to 4.8 minutes), followed by an intermediate (β) phase ($t_{½\beta}$ 0.5 to 2.6 hours) and a much slower (γ) terminal elimination phase ($t_{½\gamma}$ = 15 to 45 hours).

Epirubicin undergoes extensive tissue distribution; volume of distribution values were high and variable (13 to 52L/kg), but similar to those reported for doxorubicin. Area under the plasma concentration versus time curve values adjusted for dose were 30 to 70% higher for doxorubicin that epirubicin following single-dose intravenous administration. Following intravenous administration, epirubicin is rapidly metabolised to 2 glucuronides, plus epirubicinol and 4 aglycones. Epirubicin is eliminated primarily via the hepatobiliary system, with approximately 11 to 15% of a dose eliminated in the urine as unchanged drug and metabolites. Patients with moderate to severe hepatic dysfunction exhibited reduced clearance of epirubicin and elevated plasma drug concentrations.

5.3. Preclinical Safety Data

In animal studies epirubicin has been shown to harm the foetus and is mutagenic and carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

0.9% sodium chloride, hydrochloric acid, water for injections.

6.2. Incompatibilities

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

It can not be recommended to mix the prouct with other medicinal products.

6.3. Shelf Life

24 months

6.4. Special Precautions for Storage

Store at 2°C to 8°C.

Remove solution from vial immediately before use. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Tests of the diluted solution up to 96 hours at 2–8°C and room temperature (20–25°C) show no significant changes without protection from light.

6.5. Nature and Contents of Container

Clear vials of glass Type I Ph.Eur. with crimp cap.

1 vial containing 10mg/5ml of epirubicin HCl.
1 vial containing 50mg/25ml of epirubicin HCl.
1 vial containing 100mg/50ml of epirubicin HCl.
1 vial containing 200mg/100ml of epirubicin HCl.

6.6. Instruction for Use/Handling

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

The following protective recommendations are given due to the toxic nature of this substance.

- personnel should be trained in good technique for reconstitution and handling.
- pregnant staff should be excluded from working with this drug.
- personnel handling epirubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
- a designated area should be defined for reconstitution (preferably under a laminar flow system).

The work surface should be protected by disposable, plastic-backed, absorbent paper.

- all items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk, waste-disposal bags for high temperature incineration.

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

Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water.

All cleaning materials should be disposed of as indicated previously.

Handle according to the guidelines for cytostatics.

7. MANUFACTURER

EBEWE Pharma Ges.m.b.H. Nfg.KG
A-4866 Unterach, AUSTRIA

8. DATE OF (PARTIAL) REVISION OF THE TEXT

March 2004