## 1. NAME OF THE MEDICINAL PRODUCT

**Doxorubicin "Ebewe" 2mg/ml – Concentrate for solution for infusion**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 2mg doxorubicin hydrochloride as active ingredient.
For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Doxorubicin is used in the following indications: soft tissue and osteogenic sarcomas, Hodgkin's disease and non-Hodgkin's lymphoma, acute lymphoblastic leukaemia, acute myeloblastic leukaemia, carcinomas of the thyroid, breast, ovary, bladder, small cell bronchogenic carcinoma and neuroblastoma.
Some reports have shown that Doxorubicin may be used intravesically.
Benefits are evident in: multiple myeloma, endometrium carcinoma, carcinoma of the cervix, Wilms tumour, tumours of the head and neck, gastric cancer, cancer of pancreas, prostate, testicle and liver.

### 4.2 Posology and method of administration

Doxorubicin may be given by

- intravenous (bolus) injection over 2–5 minutes or as continuous infusion into a running infusion of sodium chloride 0.9% w/v intravenous injection, dextrose intravenous injection 5% w/v or sodium chloride and dextrose intravenous injection.

Bolus injection causes higher peak plasma-concentrations and therefore is probably more cardiotoxic.
Adult dosage
Monotherapy
Dosage depends on tumor type, cardiac or hepatic function, and concurrent chemotherapy.
The recommended dose as single agent: The commonly recommended dosage schedule as single agent is 60–75mg/m² by intravenous injection, once every three weeks. An alternative dose schedule is 20mg/m² intravenously, for three consecutive days, once every three weeks.
The maximum cumulative dose: 550mg/m² should not be exceeded.
Administration of doxorubicin in a weekly regimen has been shown to be as effective as the 3-weekly regimen whilst reducing cardiac toxicity. The recommended dosage is 20mg/m² weekly, although objective responses have been seen with doses between 6 and 12mg/m².
Combinationtherapy
Dosage should be decreased when combination with other cytostatic drugs with any similar toxicity is used.
The maximum cumulative dose: If a patient received mediastinal irradiation, has concomitant heart disease, or is also treated with other cardiotoxic, non-anthracycline oncolytics, a maximal cumulative dose of 450mg/m² is recommended.
Dosage adjustments in specific patient groups:
Hepatic dysfunction: Dosage should be reduced in patients with impaired hepatic function. Doxorubicin dosage should be reduced if the bilirubin is elevated as follows: serum bilirubin 12 to 30mg – give ½ of the normal dose, bilirubin > 30mg – give ¼ of the normal dose.
Renal dysfunction:
In general, impaired renal function does not require dose reduction.
Patients with cardiac risk:
Patients at increased risk for cardiotoxicity should be considered for treatment with a 24 hours continuous infusion, rather than bolus injection. In this way, cardiotoxicity may be less frequent, without a reduction in therapeutic efficacy. In these patients, the ejection fraction should be measured before each course.
The risk of development of cardiomyopathy gradually increases with the dosage. A cumulative lifetime dose of 450–550mg/m² should not be exceeded.
In case of preexisting heart disease or prior radiotherapy to the heart or the mediastinum, cumulative doses of more than 400mg should be avoided (Monitoring of the cardiac function – see section 4.4. Special Warnings).
In combination with other oncolytics doses of 50–75mg/m² are administered. Myelosuppression may be more pronounced because of the additive effects of the drugs.
Dosage in children
Dosage for children should be lowered since they have an increased risk of cardiotoxicity especially delayed cardiotoxicity and therefore follow-up cardiac evaluation is recommended.
Myelotoxicity should be anticipated, with nadirs at 10 to 14 days after start of treatment, but is usually followed by a rapid recovery due to the large bone marrow reserve of children as compared to adults.
Superficial bladder carcinoma and bladder carcinoma in situ
The recommended dosage is 50mg in 50ml normal saline, administered via a sterile catheter. Initially, this dose is given weekly, later on monthly. The optimal duration of treatment has not yet been determined; it ranges from 6 to 12 months.
Restrictions regarding the maximal cumulative dose, as with intravenous administration, do not apply to intravesical administration, because systemic absorption of doxorubicin is negligible.
Take care in the administration to avoid the possiblity of perivenous infiltration resulting in local necrosis and thrombophlebitis.
Doxorubicin must not be given intrathecally or intramuscularly, subcutan or by long term infusion. (Since doxorubicin is reported to form precipitates in combination with heparin and 5 -fluorouracil, it should not be mixed with any other drug.)

### 4.3 Contra-indications

Doxorubicin is contra-indicated in patients who have a marked myelosuppression (e.g. induced by previous anti-tumour treatment), in pre-existing or acute cardiac insufficiency or in patients who have previously received the maximum cumulative dose of doxorubicin or daunorubicin.
The presence of bucccal ulceration; this may be preceded by premonitory buccal burning sensations and repetition of treatment in the presence of this symptom is not advised.
During pregnancy and breast feeding.
Hypersensitivity to doxorubicin, chemically related products or any other excipient.
Doxorubicin should not be used intravesically for the treatment of bladder carcinoma in patients with urethral stenosis who can not be catheterised.
The intravesical route of administration should not be attempted in patients with invasive tumours that have penetrated the bladder wall, urinary tract infections or inflammatory conditions of the bladder.

### 4.4 Special warnings and special precautions for use

General precautions:
Doxorubicin should only be administered under the supervision of a physician experienced in the use of chemotherapy. It is recommended that the patient be hospitalised during at least the first phase of treatment since close observation and laboratory monitoring is necessary. Prior to treatment with doxorubicin, cardiac and hepatic function and haematology baseline tests should be carried out.
Nausea, vomiting and mucositis are often extremely severe and should be treated appropriately. Doxorubicin should not be administered intramuscularly or subcutaneously.
Extravasation:

Extravasation:
Extravasation results in a severe and progressive tissue necrosis. Extravasation is signified by pain and/or a burning sensation at the site of intravenous administration of doxorubicin. If extravasation occurs, the injection should be terminated immediately and restarted in another vein. Ice packs should be applied to the site of extravasation. Flooding with normal saline, local infiltration with corticosteroids, or sodium hydrogencarbonate solution (8.4%), and application of dimethylsulfoxide have been reported with varying success. Local application of hydrocortisone cream 1% may be beneficial. The advice of the plastic surgery consultant should be asked for, and wide excision of the involved area should be considered.
Cardiotoxicity:
There is an established risk of development of anthracycline induced cumulative dose dependent cardiomyopathy, therefore cumulative dose of 450–550mg/m² should not be exceeded. At doses above this the risk of development of cardiac failure increases considerably. Reduction of the cumulative dose is the most important means of avoiding doxorubicin cardiotoxicity. The cardiotoxicity of doxorubicin may manifest as tachycardia, ECG changes or cardiac failure which may occur suddenly up to several months/years after discontinuation of treatment without preceding ECG changes. The risk of developing heart failure in cancer patients treated with doxorubicin persists throughout life. Cardiac failure due to doxorubicin may be unresponsive to conventional treatment.
The risk of cardiotoxicity increases in patients previously treated with mediastinal or pericardial irradiation, in patients treated with other or previous anthracyclines and/or anthracenediones, in patients with a history of cardiac disease, in elderly patients (age ≥ 70 years) as well as in children below 15 years. Cardiotoxicity may occur at doses lower than the recommended cumulative limit. The total cumulative dose of doxorubicin to an individual patient should therefore take into account any previous or concomitant treatment with other potentially cardiotoxic drugs or therapy such as high dose IV cyclophosphamide, mitomycin C or dacarbazine, other anthracyclines such as daunorubicin, or mediastinal or pericardial irradiation.
Acute severe arrhythmias have been reported to occur during or within a few hours after doxorubicin administration.
ECG changes may occur including a reduction in the voltage of the QRS wave, and a prolongation of the systolic time interval, and the ejection fraction may be reduced.
Extreme care should be taken in patients with existing heart disease, such as a recent myocardial infarction, heart failure, cardiomyopathy, pericarditis or dysrhythmias, or in patients who have received other cardiotoxic agents such as cyclophosphamide (see section 4.5).
Monitoring of the cardiac function:
Cardiac function should be assessed prior to the start of treatment and should be carefully monitored throughout treatment and assessed after the doxorubicin therapy. An ECG before and after each treatment is recommended. Changes in ECG such as depression or negative T-wave, decrease in the ST-segment or arrhythmias are usually signs of an acute but transient (reversible) toxic effect and are not considered indications for suspension of doxorubicin therapy. However a persistent reduction in the amplitude of QRS-wave and a prolongation of the systolic interval are considered more indicative of anthracycline induced cardiotoxicity.
When the voltage of the QRS wave decreases by 30% or at a fractional shortening of 5% it is recommended that treatment be stopped.
The optimum method of prediction of cardiomyopathy is detection of a reduction of the left ventricular ejection fraction (LVEF), determined by ultrasound or a heart scintigraphy. LVEF investigation should be performed prior to treatment and repeated after each cumulative dose of 100mg/m² and at any clinical signs of cardiac failure. As a rule an absolute decrease of > 10% or a decrease below 50% in patients with normal initial LVEF-values is a sign of impairment of cardiac function. Continued treatment with doxorubicin in such patients must be carefully evaluated.
Myelosuppression:
The high incidence of bone marrow depression requires careful haematological monitoring. There is a significant risk of neutropenia, thromocytopenia and anaemia occurring less frequently. The nadir is reached between 10–14 days after administration. Blood values usually return to normal within 21 days after administration. Doxorubicin therapy should not be started or continued when polynuclear granulocyte counts are below 2000/mm³. In the treatment of acute leukaemias this limit may be set lower, depending on the circumstances.
Severe myelosuppression may result in haemorrhage or superinfection and is an indication for the reduction or suspension of doxorubicin treatment.
Because of the potential for immunosuppression, measures should be taken to prevent secondary infection.
Hyperuricaemia:
As with other cancer chemotherapeutic agents, there is a risk of hyperuricaemia resulting in acute gout or urate nephropathy following tumor lysis with regimens containing doxorubicin.
Hepatic impairment:
Since doxorubicin is excreted mainly via the liver, reduced hepatic function or failure may delay elimination and increase overall toxicity. Therefore it is recommended that hepatic function tests (SGOT, SGPT, alkalic phosphatase and bilirubin) be carried out prior to and during the treatment.
The blood uric acid level should be monitored; sufficient fluid intake should be ascertained (with a daily minimum of 3 l/m²). If necessary, a xanthine-oxidase inhibitor (allopurinol) may be administered.
Men as well as women should take effective contraceptive measures during and for at least three months after doxorubicin therapy.
Discoloration of urine:
Patients should be warned that doxorubicin may impart a red colour to the urine, particularly in the first specimen following administration, but that this is no cause for alarm.
Intravesical route:
The intravesical route of administration should not be attempted in patients with, invasive tumours that have penetrated the bladder wall, urinary tract infections, inflammatory conditions of the bladder.

**4.5 Interaction with other medicinal products and other forms of interaction**
Caution should be exercised when administering doxorubicin after or together with other cardiotoxic or anticancer (especially myelotoxic) agents as cardiotoxicity is enhanced.
Doxorubicin peak levels, terminal half-life and volume of distribution may be increased following the co-administration of verapamil.
Doxorubicin may cause exacerbations of hemorragic cystitis caused by previous cyclophosphamide therapy.
As doxorubicin is rapidly metabolised and predominantly eliminated by the biliary system, the concomitant administration of known hepatotoxic chemotherapeutic agents (e.g. methotrexate) could potentially increase the toxicity of doxorubicin as a result of reduced hepatic clearance of the drug.
High dose Cyclosporin and Doxorubicin increases the serum levels of both. This may cause an increase myelotoxicity and excessive immunsuppression.
Inhibitors of cytochrome P-450 (e.g. cimetidine and ranitidine) may decrease the metabolism of doxorubicin, with a possible increase in toxic effects. Inducers of enzyme cytochrome P-450 (e.g. rifampicin and barbiturates) may stimulate the metabolism of doxorubicin, with a possible decrease in efficacy.
Doxorubicin potentiates the effect of radiation therapy and can, even if administered some considerable time after discontinuation of the radiation therapy, cause severe symptoms in the area concerned.

**4.6 Use during pregnancy and lactation**

Reproductive studies in animals, showed that doxorubicin was teratogenic and embryotoxic (see section 5.3). Doxorubicin is secreted into breast milk. Doxorubicin should not be used during pregnancy or breastfeeding (see section 4.3.).

Doxorubicin is excreted in breast milk. Usage during lactation is therefore not recommended.

**4.7 Effects on ability to drive and use machines**

Patients who suffer from any effects that may impair driving performance (drowsiness, nausea or vomiting) should avoid driving and operating machinery.

**4.8 Undesirable effects**

ADR are very common (>10%). Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity which occur in up to >10% and 1–10% of patients respectively.

Doxorubicin may potentiate the toxicity of radiotherapy and other anticarcinogenic therapies (streptozocin, methotrexate, cyclophosphamide).

**Neoplasms benign and malignant (including cysts and polys)**

*Rare >0.01–<0.1%:*

The occurrence of secondary acute myeloid leukaemia, with or without a preleukaemic phase, has been reported rarely in patients treated with doxorubicin in association with DNA-damaging anti-neoplastic agents. Such cases may also have a short (1–3 year) latency period.

**Blood and the lymphatic system disorders**

*Very common > 10%:*

Myelosuppression includes a transient leukopenia, anemia and thrombocytopenia, reaching its nadir at 10–14 days after treatment.

**Cardiac disorders**

*Common – very common > 1% – > 10%:*

Cardiotoxicity may occur as arrhythmia directly following drug administration; ECG changes, including T-wave flattening and S-T depression, may last up to two weeks after administration.

The risk of a developing cardiomyopathy gradually increases with an increasing dosage. A cumulative dose of 450–550mg/m² should not be exceeded, but irreversible congestive heart failure may even occur with dose of 240mg/m².

Age over 70 or below 15 years should be regarded as a risk factor. Also, concomitant or previous treatment with mitomycin C, cyclophosphamide or dacarbazine has been reported to potentiate doxorubicin induced cardiomyopathy (see section 4.4.).

Cardiotoxicity may be delayed several weeks, months or even years after discontinuation of doxorubicin therapy. The risk of developing heart failure in cancer patients treated with doxorubicin persists throughout life.

**Gastrointestinal disorders**

*Very common > 10%:*

Nausea, vomiting, mucositis (as stomatitis and proctitis) and diarrhoea may occur 5 to 10 days after administration. Damage of the gastro-intestinal tract can lead to ulceration, haemorrhage and perforation.

Mucositis commonly begins with a burning sensation in the mouth and throat 5–10 days after treatment and may progress to ulceration with the associated risk of secondary infection. Mucositis may also affect the vagina, rectum and oesophagus.

**Hepato-biliary disorders**

*Common >1% – <10%:*

Slight transient increases of liver enzymes have been reported. Concomitant irradiation of the liver may cause severe hepatotoxicity, sometimes progressing to cirrhosis.

**Skin and subcutaneous tissue disorders**

*Very common > 10%:*

Reversible alopecia in the majority of patients, hyperpigmentation of nailbeds, dermal creases, onycholysis.

Doxorubicin is highly irritant and extravasation at the infusion site may cause local pain, irritation, inflammation, thrombophlebitis, even leading to serious ulceration and skin necrosis.

Hypersensitivity reactions such as cutaneous reactions (rashes, pruritus, urticaria, angiooedema, fever and anaphylaxis) have been occasionally reported.

Doxorubicin influences and potentiates normal tissue reactions to radiation. Also, late („recall") reactions may occur when doxorubicin is administered some time after irradiation.

**Renal and urinary disorders**

*Common >1%–<10%:*

Intravesical administration may cause the following adverse reactions: hematuria, vesical and urethral irritation, stranguria and polyuria. These reactions are usually of moderate severity and of short duration. Intravesical administration of doxorubicin may sometimes cause hemorrhagic cystitis; this may cause a decrease in bladder capacity. Doxorubicin causes red discoloration of the urine.

**General disorders and administration site conditions**

*Rare > 0.01 – < 0.1%:*

conjunctivitis, lacrimation.

Facial flushing may occur if the injection is given too rapidly.

Thrombophlebitis and conjunctivitis have been reported.

**4.9 Overdose**

The symptoms of an overdose are likely to be an exaggeration/extension of the pharmacological action. Fatalities due to single doses of 250mg and 500mg doxorubicin have been reported. Acute myocardial degeneration may occur within 24 hours. Severe myelosuppression may occur with peak effects 10 to 15 days after administration of doxorubicin. Cardiac failure may occur up to six months following an overdose.

Symptomatic supportive measures should be adopted in cases of overdosage.

As soon as possible the appropriate measures should be taken, such as the administration of heart glycosides and diuretics.

Treatment of possible haemorrhage and of infections due to severe myelo- or immuno-suppression may be necessary. Blood transfusions and reverse barrier nursing may be required.

Haemodialysis is of no benefit as doxorubicin is mostly excreted in the biliary tract and by the intestine.

## 5. PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamic properties**

ATC classification: L01D B01

Doxorubicin has been shown to have antineoplastic activity in several animal models and is effective in humans but there is as yet no consensus as to how doxorubicin and other anthracyclines exert their anti tumour activity. Three principal biochemical mechanisms have been proposed: DNA intercalation, membrane binding and metabolic activation via reduction.

An important cause of treatment failure with doxorubicin and other anthracyclines is the development of resistance. In an attempt to overcome cellular resistance to doxorubicin the use of calcium antagonists such as verapamil has been considered since the primary target is the cell membrane; verapamil inhibits the slow channel of calcium transport and can enhance cellular uptake of doxorubicin. Chang et al, 1989 have shown that the cytotoxicity of doxorubicin is potentiated by verapamil in vitro using three pancreatic cancer cell lines.

They also investigated a possible role of its major reduction metabolite, doxorubicinol, which occurs in human plasma, but concluded that it was not involved in the intracellular accumulation/retention of doxorubicin. It should be noted that a combination of doxorubicin and verapamil has been shown to be associated with severe toxic effects in animal experiments. (Sridhar et al, 1992).

**5.2 Pharmacokinetic properties**

The intravenous administration of doxorubicin is followed by a rapid plasma clearance ($t_{1/2}$ = 10 min.) and significant tissue binding. The terminal half-life is approximately 30 hours.
Doxorubicin is partly metabolised, mainly to doxorubicinol and to a lesser extent, to the aglycon, and is conjugated to the glucuronide and sulfate. Biliary and fecal excretion represents the major excretion route. About 10% of the dose is eliminated by renal excretion.
Plasma protein binding of doxorubicin ranges from 50–85%. The volume of distribution is 800–3500L/m².
Doxorubicin is not absorbed after oral administration; it does not cross the blood-brain barrier.
Impairment of liver function may decrease the clearance of doxorubicin and its metabolites.

**5.3 Preclinical safety data**

The $LD_{50}$ after a single intravenous bolus injection of doxorubicin to rats, mice and rabbits were 12.6, 9.4 and 6mg/kg, respectively.
Reduction in body weights and survival times were seen in old and young rats administered a single intravenous dose of 2.5 and 5mg/kg, respectively.
The animal data show an increased toxicity in elder rats.
As expected from its interaction with DNA and cytotoxic properties doxorubicin is mutagenic, showing chromosome damage in vitro in human lymphocytes and is also carcinogenic in animals. The compound is also teratogenic and embryocidal. Although i.v. and i.p. dosage to mice and rats at doses up to 1mg/kg from days 7 to 13 of gestation produced no evidence of teratogenicity a higher dose of 2mg/kg i.p. for longer to rats caused atresia of the oesophagus and intestine and cardiovascular abnormalities. In rabbits dosed i.v. at up to 0.6mg/kg on days 16–18 abortions occurred but there were no foetal abnormalities. Post-natal renal damage was produced in rats dosed with 1 or 1.5mg/kg of doxorubicin during days 6–9 or 10–12.
Microscopic examination of the heart of patients shows evidence of a severe cardiomyopathy and a variety of alterations have been described the majority of which have been reproduced in animal models in the mouse, rat, rabbit, dog and monkey; the development and character of the lesions in the rat and rabbit closely resemble those in humans although rats develop cardiomyopathy at lower total doses than rabbits. The pathogenesis is difficult to assess since a large number of complex biochemical effects have been shown to occur in the heart.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Hydrochloric acid, sodium chloride, water for injection.

**6.2 Incompatibilities**

Contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug. Doxorubicin should not be mixed with heparin and 5-fluororuacil as a precipitate may form and it is not recommended that doxorubicin be mixed with other drugs.

**6.3 Shelf life**

24 months

**6.4 Special precautions for storage**

Store at 2–8°C. Protect from light, therefore store the vial in the carton. 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 24 hours at 2–8°C show no significant changes with or without protection from light.

**6.5 Nature and contents of the container**

Vials of Ph.Eur. Type I clear glass with grey teflon-coated chlorobutyl rubber stopper and aluminium crimp cap, packed in a carton.

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

**6.6 Instructions for use/handling**

For single use only.
Observe guidelines for handling cytotoxic drugs.
The following protective recommendations are given due to the toxic nature of this substance:

- Personnel should be trained in good techinque for handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling doxorubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
- All items used for administration or cleaning, including gloves, should be placed in high risk waste disposal bags for high temperature (700°C) 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 chlorite) solution, preferably soaking overnight and then rinse with water.
All cleaning materials should be disposed of as indicated previously.
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 (see section 4.2.).
Because of the various existing dosage schemes the use is only recommended under the direction of those experienced in cytotoxic therapy.

## 7. MANUFACTURER

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## 8. DATE OF (PARTIAL) REVISION OF THE TEXT

September 2004