Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

DEBDOX 50mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 50 mg of doxorubicin hydrochloride (to be reconstituted with 25 ml)
After reconstitution each ml contains 2 mg of doxorubicin hydrochloride.

Excipients
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion
Red-orange, sterile powder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Breast cancer
- Neoadjuvant and adjuvant therapy of osteosarcoma
- Advanced soft-tissue sarcoma in adults
- Small-cell lung cancer (SCLC)
- Hodgkin’s lymphoma
- Highly malignant non-Hodgkin’s lymphoma
- Induction and consolidation therapy in acute lymphatic leukaemia
- Acute myeloblastic leukaemia
- Advanced multiple myeloma
- Advanced or recurrent endometrial carcinoma
- Advanced or relapsed papillary/follicular thyroid cancer
- Anaplastic thyroid cancer
- Systemic treatment of local advanced or metastasized bladder carcinoma
- Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection
- Recurrent ovarian carcinoma
- Wilms’ tumour (in stage II in highly malignant variants, all advanced stages [III – IV])
- Advanced neuroblastoma
- Ewing´s sarcoma

Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs.

4.2 Posology and method of administration

DEBDOX should be administered only under the supervision of a qualified physician experienced in cytotoxic therapy. Also, patients must be carefully and frequently monitored during the treatment.

Due to the risk of an often lethal cardiomyopathy, the risks and benefits to the individual patient should be weighted before each application.

Prior to start of the treatment it is recommended to measure the liver function by using conventional tests such as AST, ALT, ALP and bilirubin as well as the renal function (see section 4.4).

Analysis of LVEF using ultrasound or heart scintigraphy should be performed in order to assess the heart condition of the patient. This control should be made prior to the start of the treatment and after each accumulated dose of approximately 100 mg/m^2 (see section 4.4).

DEBDOX 2 mg/ml powder for concentrate for solution for infusion should be reconstituted with 25 ml of 9 mg/ml (0.9 %) sodium chloride solution for infusion or water for injections, to a concentration of 2 mg/ml. For more details on reconstitution and dilution, see section 6.6.

Intravenous (i.v.) administration of doxorubicin must be given with great care and it is advisable to give the drug via the tubing of a freely running i.v. saline or 5 % glucose within 3-5 minutes. This method minimises the risk of thrombosis development and perivenous extravasation that result in severe cellulitis, vesication and tissue necrosis. Doxorubicin can be administered intravenously as a bolus within minutes, as a short infusion for up to an hour or as continuous infusion for up to 24 hours. A direct intravenous injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

DEBDOX should not be administered by the intramuscular, subcutaneous, oral or intrathecal route.

Intravenous administration:
The dose is usually calculated based on body surface area (mg/m^2). Dosage schedule of doxorubicin administration may vary according to indication (solid tumours or acute leukemia) and according to its use in the specific treatment regimen (as a single agent or in combination with other cytotoxic agents or as a part of multidisciplinary procedures that include combination of chemotherapy, surgical procedure and radiotherapy and hormonal treatment).

Monotherapy:
The recommended dose is 60-75 mg/m^2 body surface i.v. as a single dose or in divided doses on 2-3 consecutive days administered intravenously at 21 day intervals. Dosage schedule and dosages may be adjusted according to the protocol. For exact information on posology, refer to current protocols.

Combination therapy:
When Doxorubicin Hydrochloride is administered in combination with other cytostatics, the dosage should be reduced to 30-60 mg/m^2 every 3 to 4 weeks.

Maximal cumulative dose:
The maximum total dose of 450−550 mg/m^2 body surface area should not be exceeded (including use with related drugs such as daunorubicin).
Patients with concomitant heart disease receiving mediastinal and/or heart irradiation, prior treatment with alkylating agents, and high-risk patients (i.e. patients with arterial hypertension for a period exceeding 5 years; with prior coronary, valvular or myocardial heart damage; or aged over 70 years) should not exceed a maximum total dose of 400 mg/m^2 body surface area and the cardiac function of these patients should be monitored (see section 4.4).

Special population groups:

Immunosuppressed patients:
The dose should be reduced in case of immunosuppression, an alternative dosage is 15-20 mg/m^2 body surface per week.

Patients with impaired hepatic function:
In the case of decreased liver function, the dosage should be reduced according to the following table:

Serum bilirubin	Recommended dose
20-50 µmol/L	½ normal dose
> 50-85 µmol/L	¼ normal dose

Doxorubicin is contraindicated in patients with severe liver function disorder (see section 4.3).

Patients with impaired renal function:
In patients with renal insufficiency (GFR less than 10 ml/min), 75% of the planned dose should be administered.

Patients with risk of cardiac impairment:
Patients with an increased risk for cardiac toxicity should be considered for treatment with a 24 hours continuous infusion of single dose, rather than injection. In this way, cardiac toxicity may be less frequent, without a reduction in therapeutic efficacy. In these patients, the ejection fraction should be measured before each course.

Patients with limited bone marrow reserve:
The dosages may be reduced in patients with a history of treatment with myelosuppressive agents. Their bone marrow reserve may be insufficient.

Obese patients:
A reduced starting dose or prolonged dose interval might need to be considered in obese patients (see 4.4 ‘Special warnings and precautions for use’).

Elderly:
The dosages may be reduced in elderly patients.

Paediatric population:
In view of the substantial risk of doxorubicin induced cardiotoxicity during childhood certain maximum cumulative dosages that depend on the youth of patients should be applied. In children (under 12 years of age) the maximal cumulative dose is usually considered 300 mg/m^2, whereas in adolescents (over 12 years of age) the maximal cumulative dose is set to 450 mg/m^2. For infants the maximal cumulative dosages are still indecisive, but even lower tolerability is assumed.

Dosage for children should be reduced, since they have an increased risk for cardiac toxicity especially late. Myelotoxicity should be anticipated, with nadirs at 10 to 14 days after start of treatment. Please refer to current treatment protocols and the specialists literature.

Note: Posology of liposomal Doxorubicin and (conventional) doxorubicin are different. The two formulations cannot be used interchangeably.

Intravesical administration:
Doxorubicin hydrochloride can be given by intravesical instillation for treatment of superficial cancer of the bladder and to prevent relapse after transurethral resection (T.U.R). The recommended dose for intravesical treatment of superficial cancer of the bladder is 30-50 mg in 25-50 ml of physiological saline per instillation. The optimal concentration is about 1 mg/ml. The solution should remain in the bladder for 1-2 hours. During this period the patient should be turned 90° every 15 minutes. To avoid undesired dilution with urine the patient should be informed not to drink anything for a period of 12 hours before the instillation (this should reduce the production of urine to about 50 ml/h). The instillation may be repeated with an interval of 1 week to 1 month, dependent on whether the treatment is therapeutic or prophylactic.

4.3 Contraindications

Hypersensitivity to doxorubicin, other anthracyclines or anthracenediones or one of the excipients.

Contraindications for intravenous administration:
- marked persisting myelosuppression and/or severe stomatitis induced by previous cytotoxic treatment and/or radiation (including patients with a high risk of haemorrhage)
- acute systemic infection
- severe impaired liver function
- severe arrhythmia, impaired heart function, acute myocardial infarction, previous myocardial infarction, acute inflammatory heart disease
- previous treatment with anthracyclines with maximal cumulative doses

- breast-feeding

Contraindications for intravesical administration:
- invasive tumours that have penetrated the bladder (beyond T_1)
- urinary tract infections
- inflammation of the bladder
- problems with catheterization
- haematuria
- breast-feeding

4.4 Special warnings and precautions for use

General warnings
Doxorubicin should be administered only under the supervision of a qualified physician experienced in cytotoxic therapy. Also, patients must be carefully and frequently monitored during the treatment.
A careful control of possible clinical complications should be performed, particularly in elderly patients, in patients with a history of heart disease, or with bone-marrow suppression, or patients who previously have been treated with anthracyclines, or treated with radiation in the mediastinum.

Before or during treatment with doxorubicin the following monitoring examinations are recommended (how often these examinations are done will depend on the general condition of the patient, the dose and the concomitant medication being taken):
- radiographs of the lungs and chest and ECG
- regular monitoring of heart function (LVEF by e.g. ECG, UCG and MUGA scan)
- daily inspection of the oral cavity and pharynx for mucosal changes
- blood tests: haematocrit, platelets, differential white cell count, SGPT, SGOT, LDH, bilirubin, uric acid.

Doxorubicin should not be administered by the intramuscular, subcutaneous, oral or intrathecal route.

The patient should be informed that the urine might be reddish after administration.
Nausea, vomiting and mucositis are often extremely severe and should be treated appropriately.

Cardiotoxicity:
When the maximum total cumulative dose is exceeded (adults 550 mg/m² BSA, in cases of prior thorax radiation therapy or during concomitant alkylating therapy 400 mg/m² BSA), the rate of anthracycline-induced cardiomyopathy increases rapidly even without pre-existing risk factors. Cardiotoxicity was, however, observed at much lower total doses in isolated cases. After a total cumulative dose of 550 mg/m² BSA, patients have, for instance, an about 5% risk of developing serious heart failure.
The cumulative dose has to be considered when the medicinal product is used in children who tolerate lower life-time total doses on the whole and in whom additional radiation therapy, young age on the beginning of therapy, and aggressive concomitant therapies result in a particularly high risk that they develop late, life-threatening cardiac organ toxicity with ventricular dysfunction, heart failure and/or arrhythmia. Girls, in comparison with boys, moreover seem to be particularly predisposed to developing delayed cardiotoxicity after a therapy with doxorubicin.
Particular caution is also indicated in children younger than 2 years and in patients with cardiologic pre-treatment (coronary heart disease, heart failure) as well as in a chronological relation with hyperthermic therapy.
Before, during and after chemotherapy with doxorubicin, the cardiac function should be monitored by means of ECG, ECHO and MUGA scan.

Myelosuppression:
If serious myelosuppression is present, doxorubicin should not be used; a dose reduction or a delay in administration is then necessary.
Care has to be taken to ensure that a serious infection and/or episode of haemorrhage can be treated fast and effectively.
Existing infections should be treated before a therapy with doxorubicin is initiated.

Gastrointestinal disorders:
An antiemetic prophylaxis is recommended.

Note: Doxorubicin should not be used in the presence of inflammations, ulcerations or diarrhoea.

Control of blood values:
Before every treatment cycle total and differential leukocyte count, erythrocyte and thrombocyte counts should be performed. Bone-marrow suppression induced by Doxorubicin hydrochloride, primarily affecting the leukocytes, requires a thorough haematological monitoring since severe myelosuppression may lead to superinfections and bleedings. Severe leucopenia may appear at doses recommended for treatment of solid tumours (a number of leukocytes of 1 000/mm^3 or lower is expected during full dose treatment with Doxorubicin hydrochloride). The leucopenia is most pronounced 10 – 14 days after the treatment and leukocytes have in most cases returned to normal at day 21. Treatment may not be started or continued when polynuclear granulocytes are less than 2000/mm^3. With treatment of acute leukaemias this value may be adjusted lower, depending on the circumstances. Also regular hematologic examination is required because of the risk of secondary leukaemia after treatment with oncolytic agents. A remission of acute leukaemia may be realized if diagnosed in an early phase and treated with the appropriate chemotherapeutic schedules.

Control of heart function:
There is a known risk of development of anthracycline induced cumulative dose-dependent cardiomyopathy. Therefore a cumulative dose of 450-550 mg/m^2 should not be exceeded. At doses above this, the risk of development of heart failure considerably increases. Doxorubicin-induced cardiotoxicity usually occurs during treatment or within two months after discontinuation of treatment, but occurrences of late complications (from months to years after treatment) have been reported. The heart function should therefore be assessed before start of the treatment and carefully monitored during the whole treatment. Electrocardiography before and after each treatment cycle 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 reduction in the amplitude of the QRS-wave and a prolongation of the systolic time interval are considered more indicative of anthracycline-induced cardiac toxicity.

The best sign to predict cardiomyopathy is a reduction in the left ventricular ejection fraction (LVEF), determined by ultrasound or heart scintigraphy. LVEF-investigations should be performed before treatment and be repeated after each accumulated dose of about 100 mg/m2, and at clinical signs of heart failure. As a rule, an absolute decrease with ≥10% or a decrease below 50%, in patients with normal initial LVEF-values, is a sign of an impairment of the heart function. Continued treatment with doxorubicin must in these cases be carefully evaluated. The risk for cardiotoxicity may increase in patients previously on radiotherapy towards the mediastinal pericardium, in patients previously treated with other anthracyclines and/or anthracenediones, in patients aged over 70 or below 15 years, or in patients with a history of heart diseases. The total dose of doxorubicin administered to the individual patient should also take into account any previous or concomitant therapy with other potentially cardiotoxic agents such as high-dose i.v. cyclophosphamide, mediastinal irradiation or related anthracycline compounds such as daunorubicin.
Acute severe arrhythmias have been reported to occur during or within a few hours after doxorubicin administration.

Cardiac symptoms may also manifest during pregnancy in women that have been treated with doxorubicin in the past (up to 20 years), even if they did not have signs of cardiac adverse events before. Cases of congestive heart failure and pulmonary oedema have been reported. Women that have been treated with doxorubicin in the past and who become pregnant should be monitored for cardiac adverse events. See also section 4.8.

Control of liver function:
Doxorubicin is mainly eliminated via the hepatobiliary system. The elimination of the drug can therefore be prolonged with subsequent general toxicity if the liver function is impaired or biliary secretion is obstructed. Before start and during treatment, control of the liver function with conventional tests such as AST, ALT, ALP and bilirubin is recommended as dose adjustment may be necessary (see section 4.2). In patients with severe hepatic impairment the risk-benefit of doxorubicin treatment should be evaluated before administration. In patients with previous radiotherapy to the mediastinal area severe hepatotoxicity has been reported, sometimes leading to death.

Secondary Leukaemia:
Secondary leukaemia (sometimes) with or without a preleukaemic phase was observed in patients who were treated with anthracyclines (including doxorubicin). Secondary leukaemia occurs more frequently if the drug is given in combination with DNA-altering cytostatics (e.g. alkylating substances, platinum derivatives) or radiation therapy, if the patients had received an intense prior therapy with cytotoxic drugs, or if the dosage of anthracyclines was raised. These cases might have a short latency period, 1-3 years.

Control of serum uric acid:
During therapy serum uric acid may increase. In case of hyperuricemia antihyperuricemic therapy should be initiated. The blood uric acid level should be monitored; sufficient fluid intake should be ascertained (with a daily minimum of 3 l/m^2). If necessary a xanthine-oxidase inhibitor (allopurinol) may be administered.

In patients with severely impaired renal function dose reductions may be necessary (see section 4.2).

Intravesical administration:
Intravesical administration of doxorubicin may cause symptoms of chemical cystitis (i.e. dysuria, urinary frequency, nocturia, stranguria, haematuria, necrosis of the bladder wall).
Special attention is needed in case of catheter problems (i.e. urethral obstruction caused by invasion of intravesical tumour).
Intravesical administration is contraindicated for tumours that have penetrated the bladder (beyond T1).
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.

Radiotherapy:
Special caution is mandatory for patients who have had radiotherapy previously, are having radiotherapy concurrently or are planning to have radiotherapy. These patients are at special risk of local reactions in the radiation field (recall phenomenon) if Doxorubicin is used. Severe, sometimes fatal, hepatotoxicity (liver damage) has been reported in this connection. Prior radiation to the mediastinum increases the cardiotoxicity of doxorubicin. The cumulative dose of 400 mg/m^2 must not be exceeded especially in this case.

Combination with other anticancer chemotherapies:
Doxorubicin hydrochloride may potentiate the toxicity of other anticancer chemotherapies (see section 4.5).
Doxorubicin potentiates the radiation toxicity to cardiac muscle, mucosa, skin and liver.

Carcinogenesis, mutagenesis and impairment of fertility:
Doxorubicin was genotoxic and mutagenic in in vitro and in vivo tests.
In women, doxorubicin may cause infertility during the period of drug administration. Doxorubicin may cause amenorrhoea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.
Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing doxorubicin treatment should use effective contraceptive methods. Men being treated with doxorubicin are advised not to father a child during and up to 6 months after treatment and to seek advise on cryo-conservation (or cryo-preservation) of sperm prior to treatment because of the possibility of reversible infertility due to therapy with doxorubicin. Women should not become pregnant during and up to 6 months after treatment.

Extravasation:
A stinging or burning sensation at the site of administration may signify a small degree of extravasation. Extravasation results in a severe and progressive tissue necrosis. If extravasation is suspected or occurs, the injection should be discontinued and restarted in a different blood vessel. Cooling the area for 24 hours can reduce the discomfort. The patient should be carefully monitored for several weeks. Surgical measures might be necessary.

Vaccines:
Vaccines are not recommended (see section 4.5). During treatment with Doxorubicin hydrochloride patients should avoid contact with recently polio vaccinated persons.

Other:
The systemic clearance of doxorubicin is reduced in obese patients (i.e. >130 % ideal body weight) (see section 4.2 Posology and Method of Administration).

4.5 Interaction with other medicinal products and other forms of interaction

Doxorubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-fluorouracil, cyclophosphamide or paclitaxel) or with products affecting cardiac function (like calcium antagonists). When doxorubicin is used together with the above mentioned agents, cardiac function must be followed carefully.

The use of trastuzumab in combination with anthracyclines (such as doxorubicin) is associated with a high cardiotoxic risk.
If possible, physicians should avoid anthracycline-based therapy for up to 24 weeks after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully. Concurrent use of anthracyclines and trastuzumab should be restricted to a well-controlled clinical trial setting with cardiac monitoring. Patients who have previously received anthracyclines are also at risk of cardiotoxicity with trastuzumab treatment, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.

(Pre-) treatment with drugs affecting the function of the bone marrow (e.g. cytostatic agents, sulfonamides, chloramphenicol, phenytoin, amidopyrine derivates, antiretroviral drugs) might lead to severe hematopoetic disturbances. The dosage of doxorubicin has to be changed if necessary. The toxic effects of a doxorubicin therapy may be increased in a combination with other cytostatics (e.g. cytarabine, cisplatin, cyclophosphamide).

Doxorubicin hepatoxicity may be enhanced by other hepatoxic treatment modalities (e.g. 6-mercaptopurine).

Doxorubicin hydrochloride used in combination with ciclosporin might require dose-adjustment. At concomitant administration of ciclosporin, the clearance of doxorubicin is reduced by approximate 50%. The doxorubicin AUC is increased by 55% and AUC of doxorubicinol by 350%. With this combination a 40% dose reduction of doxorubicin is suggested. Ciclosporin inhibits, similar to verapamil, both CYP3A4 and P-glycoprotein, which might explain the interaction and resulting increase in adverse effects.

Cytochrome P-450 inhibitors (e.g. cimetidine) also reduce the plasma clearance and increase the AUC of doxorubicin, possibly by similar mechanisms as suggested for ciclosporin, and may thus lead to an increase in adverse effects. Conversely, cytochrome P-450 inducers (e.g. phenobarbital and rifampicin) decrease Doxorubicin plasma levels and may thus lead to a decrease in efficacy.

Doxorubicin is a potent, radiosensitizing agent ("radiosensitizer"), and recall phenomena induced by it may be life-threatening. Any preceding, concomitant or subsequent radiation therapy may increase the cardiotoxicity or hepatotoxicity of doxorubicin. This applies also to concomitant therapies with cardiotoxic or hepatotoxic drugs. If a doxorubicin therapy follows a treatment with cyclophosphamide, this may not only increase cardiotoxicity, but also aggravate haemorrhagic cystitis.

If paclitaxel is given before doxorubicin, this may result in an elevated plasma concentration of doxorubicin and/or its metabolites. There are data suggesting that this effect is lower if the anthracycline is given before paclitaxel.

Doxorubicin therapy may lead to increased serum uric acid, therefore dose adjustment of uric acid lowering agents may be necessary.

Doxorubicin may reduce oral bioavailability of digoxin.

The absorption of antiepileptic drugs (e.g. carbamazepine, phenytoin, valproate) is decreased after concomitant use of Doxorubicin hydrochloride.
During treatment with Doxorubicin hydrochloride patients should not be actively vaccinated and also avoid contact with recently polio vaccinated persons.

Doxorubicin binds to heparin and 5-fluorouracil. Precipitations and loss of action of both substances are therefore possible. See 6.2 for more details.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Doxorubicin should not be given during pregnancy. In general cytostatics should only be administered during pregnancy on strict indication, and the benefit to the mother weighed against possible hazards to the foetus. In animal studies, doxorubicin has shown embryo-, feto- and teratogenic effects (see section 5.3).
Men and women should use effective contraception during and up to 6 months after treatment (see section 4.4).

Lactation:
Doxorubicin has been reported to be excreted in human breast milk. A risk to the suckling child cannot be excluded. Since the use of doxorubicin during breast-feeding is contraindicated, breast-feeding should be discontinued during treatment with doxorubicin (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, as nausea and vomiting are frequent, patients should be warned against driving and using machines.

4.8 Undesirable effects

Treatment with doxorubicin often causes undesirable effects, and some of these effects are serious enough to entail careful monitoring of the patient. The frequency and kind of undesirable effects are influenced by the speed of administration and the dosage. Bone-marrow suppression is an acute dose limiting adverse effect, but is mostly transient. Clinical consequences of doxorubicin bone marrow/haematological toxicity may be fever, infections, sepsis/septicaemia, septic shock, haemorrhages, tissue hypoxia or death. Nausea and vomiting as well as alopecia are seen in almost all patients.
Intravesical administration may cause the following adverse reactions: hematuria, vesical and urethral irritation, stranguria and pollakisuria. These reactions are usually of moderate severity and of short duration.
Intravesical administration of doxorubicin may cause a sometimes hemorrhagic cystitis; this may cause a decrease in bladder capacity.

Extravasation can lead to severe cellulitis, vesication, thrombophlebitis, lymphangitis and local tissue necrosis which may require surgical measures (including skin grafts).

Adverse reactions are listed below by system organ class and absolute frequency (all reported events). Frequencies are defined as: Very common (≥ 1/10), common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

	Very common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations			Sepsis, septiciaemia			
Neoplasms benign and malignant			Acute lymphocytic leukaemia. Acute myelogenic leukaemia.			
Blood and lymphatic system disorders	Myelosuppression including leukopenia, neutropenia, thrombocytopenia, anaemia.*					
Immune System				Anaphylactic		

disorders				reactions.		
Endocrine disorders					Amenorrhoea Hot flashes. Oligospermia Azoospermia.	
Metabolism and nutrition disorders					Hyperuricaemia.	
Eye disorders						Conjunctivitis/keratitis, increased lachrymation.
Cardiac disorders	Cardiotoxicity**	Life-threatening congestive (dilatative) cardiomyopathy (after cumulative dose of 550 mg/m²), sinus tachycardia, ventricular tachycardia, tachyarythmia, supraventricular and ventricular extrasystoles, bradycardia, arrhythmia. Asymptomatic reduction of the left ventricular ejection fraction.			Unspecific ECG changes (ST changes, low voltage, long QT intervals). Isolated cases of life-threatening arrhythmias, acute left ventricular failure, pericarditis, fatal pericarditis-myocarditis syndrome. Atrio ventricular block, bundle branch block.	
Vascular disorders		Haemorrhage			Thromboembolism	
Respiratory, thoracic and mediastinal disorders						Bronchospasm.
Gastrointestinal disorders	Gastrointestinal disturbance***, Diarrhoea. Nausea and vomiting. Mucositis, stomatitis, oesophagitis.	Anorexia	Gastrointestinal haemorrhage. Abdominal pain. Necrosis of the large intestine with massive haemorrhage and severe infections.		Gastric erosions/ulcers.Ulceration of the mucous membranes (mouth, pharynx, oesophagus, gastrointestinal tract). Hyperpigmentation of the oral mucous membrane.	
Hepatobiliary disorders						Hepatotoxicity (sometimes progressing to cirrhosis). Transient increase of liver enzymes.
Skin and subcutaneous tissue disorders	Alopecia (dose-dependent and in most cases reversible). Reddening. Photosensitization.	Local hypersensitivity reactions in the field of radiation (“radiation recall reaction”). Itching.		Urticaria. Exanthema. Hyperpigmentation of skin and nails. Onycholysis. Extravasation (may lead to severe cellulites, vesication, thrombophlebitis, lymphangitis, and local tissue necrosis).	Acral erythemas. Blistering. Palmar-plantar erythrodysaesthesia.	Actinic keratosis
Musculoskeletal, connective tissue and bone disorders						Arthralgia.
Renal and	Red coloration to	Dysuria,			Acute renal failure	

urinary disorders	the urine	Chemical cystitis following intravesical treatment (with symptoms such as vesical irritation, urethral irritation, dysuria, stranguria, pollakisuria, haematuria, vesicular spasms, hemorrhagic cystitis).			(isolated cases). Hyperuricaemia and subsequent uric acid nephropathy as a consequence of massive tumour lysis.	
General disorders and administration site conditions	Fever		Dehydration	Shivering. Dizziness. Injection site reactions (local erythematous reactions along the vein, pain, phlebitis, phlebosclerosis).		
Surgical and medical procedure						Radiation damage (skin, lungs, oesophagus, gastrointestinal mucosa, heart) that is already healing may reappear following doxorubicin administration.

*Myelosuppression is one of the dose-limiting side-effects and may be serious. It manifests mainly in the decrease of the leukocyte count. Leucopoenia was observed in almost 75 % of the patients with an adequate bone marrow reserve who were treated with 60 mg/m² BSA every 21 days. Although less frequently, thrombocytopenia, neutropenia, and anaemia were also reported. Superinfections (very frequent) and haemorrhage were likewise observed in connection with the appearance of bone marrow suppression. Myelosuppression usually culminates 10 to 14 days after the administration of doxorubicin and subsides between the 21st and 28th day in most cases. If appearing, thrombocytopenia or anaemia occurs in the same period, but is usually less severe (see section 4.4).

** Doxorubicin is cardiotoxic. The risk that the cardiotoxic side-effects become manifest is elevated during and after radiation therapy of the mediastinal region, after a pre-treatment with potentially cardiotoxic agents (e.g. anthracyclines, cyclophosphamide), and in elderly patients (over 60 years) and patients with manifest arterial hypertension (see section 4.4).
The cardiotoxic effect of doxorubicin can manifest in two types:

Acute type
The acute-type side-effects occur mostly within the first 24 to 48 hours after initiation of therapy, are not dose-dependent and are characterized by the following symptoms: temporary arrhythmia (frequent), especially sinus tachycardia (frequent), and supraventricular and ventricular extrasystoles. They are (very rarely) characterized by unspecific ECG changes (ST changes, low voltage, and long QT intervals). These changes are generally reversible, and their appearance is no contraindication for the repeated use of doxorubicin. However, life-threatening arrhythmias may occur during, or few hours after, the use of doxorubicin; in isolated cases, acute left ventricular failure, pericarditis or fatal pericarditis-myocarditis syndrome was reported.

Delayed type
The delayed-type side-effects are manifestations of dose-dependent cumulative organ toxicity, which is generally irreversible and often life-threatening. They often manifest as congestive (dilatative) cardiomyopathy with the signs of left ventricular failure within few months of the termination of the therapy. Cardiotoxicity may, however, become manifest for the first time as late as several years after the termination of the therapy; its incidence increases with the total cumulative dose (see section 4.4).

*** The emetogenic potential of doxorubicin is high; relatively severe nausea and vomiting occur in about 80 % of the patients on the first day of therapy, but also later (see section 4.4).

4.9 Overdose

No specific antidote for doxorubicin is known.
An acute intoxication can become manifest within 24 hours as, e.g., heart failure with chest pain, angina pectoris and myocardial infarction. A cardiologist has to be consulted in such cases. Other signs of overdose are severe myelosuppression, which usually occurs 10 to 14 days after the beginning of therapy, and severe inflammation of the mucous membranes. Pronounced myelosuppression has to be treated in a hospital. According to the circumstances, the treatment can include the substitution of the lacking components and antibiotic therapy. Referring the patient to a germ-free room may be necessary. If signs of intoxication occur, the administration of doxorubicin should be discontinued at once. The signs of chronic intoxication are in particular the above-mentioned signs of cardiotoxicity. If heart failure occurs, a cardiologist has to be consulted.
A haemodialytic therapy is probably useless in intoxications with doxorubicin because doxorubicin has a very large volume of distribution and only 5 % of a dose is eliminated by the kidneys.

Extravasation
Perivenous misinjection results in local necrosis and thrombophlebitis. A burning sensation in the region of the infusion needle is indicative of perivenous administration.
If extravasation occurs, the infusion or injection has to be stopped at once; the needle should be left in place for a short time and then be removed after short aspiration.
In case of extravasation start intravenous infusion of dexrazoxane, no later than 6 hours after extravasation (see the SmPC of dexrazoxane for dosing and further information). In case dexrazoxane is contraindicated, it is recommended to apply 99 % dimethylsulfoxide (DMSO) locally to an area twice the size of the area concerned (4 drops to 10 cm^2 of skin surface area) and to repeat this three times a day for a period of no less than 14 days. If necessary, débridement should be considered. Because of the antagonistic mechanism, the area should be cooled after the application of DMSO (vasoconstriction vs. vasodilatation), e.g., to reduce pain.
Do not use DMSO in patients who are receiving dexrazoxane to treat anthracycline-induced extravasation.
Other measures have been treated controversially in the literature and have no definite value.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthracyclines and related substances, ATC code: L01D B01

Doxorubicin belongs to the group of anthracyclines and is a cytostatic antibiotic that has been isolated from cultures of *Streptomyces peucetius var. caesius.* It is now prepared semi-synthetically from daunorubicin. Doxorubicin is a strong tissue irritant.

The biological activity of doxorubicin is attributed to its DNA-binding property, which results in inhibition of the enzymatic system, vital for the DNA-replication and the DNA-transcription. The blocking of the cellular cycle seems to be maximal during S phase and mitosis, but inhibition has also been observed during other cell cycle phases.

5.2 Pharmacokinetic properties

After intravenous administration, doxorubicin elimination is characterized by a tri-phasic elimination from plasma with a terminal half life of approximately 30 hours. The distribution volume is approximately 25 L/kg. The degree of protein binding in plasma is approximately 70 %.

Highest drug concentrations are attained in the lung, liver, spleen, kidney, heart, small intestine and bone-marrow. Doxorubicin does not cross the blood-brain barrier.

Doxorubicin is rapidly metabolised, and the main metabolite is the less active 13-dihydroderivative doxorubicinol. Within five days approximately 5% is recovered in the urine, whilst 40-50% is excreted through the bile within 7 days. Reduced liver functions results in a slower elimination of the substance.

5.3 Preclinical safety data

Animal studies from literature show that doxorubicin affects the fertility, is embryo- and fetotoxic and teratogenic. Other data shows that doxorubicin is mutagenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

6.2 Incompatibilities

Doxorubicin must not be mixed with heparin, as this will result in precipitation. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Incompatibilities with the following products have been reported:
Aminophyllin, cephalotin, dexamethasone, fluorouracil, hydrocortisone.

6.3 Shelf life

Vial before opening:
3 years

Reconstituted product
The reconstituted product should be diluted immediately after reconstitution.

Product diluted in 0.9 % sodium chloride solution
The chemical and physical in-use stability after dilution to the concentration range of 0.05 mg/ml and 0.5 mg/ml has been demonstrated for 24 hour when stored at room temperature (15-25 °C). This infusion preparation in 0.9% saline should not be stored at 2-8°C.

From a microbiological point of view, this infusuion preparation should used immediately.

Product diluted in 5 % glucose solution
The chemical and physical in-use stability after dilution to the concentration range of 0.05 mg/ml and 0.5 mg/ml has been demonstrated for 72 hours when stored at room temperature (15-25 °C).

From a microbiological point of view, this infusion preparation 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 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

No special storage conditions.
For storage conditions of the reconstituted/diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

DEBDOX powder for concentrate for solution for infusion is supplied as a red-orange, sterile, lyophylized powder, in injection vials.

The vials are colourless, type I glass with a bromobutyl rubber stopper and an aluminium seal covered with a coloured polypropylene disc.

DEBDOX is available in cartons containing 1 vial of 50 mg of doxorubicin hydrochloride.

6.6 Special precautions for disposal and other handling

DEBDOX 2 mg/ml powder for concentrate for solution for infusion should be reconstituted with 25 ml of 9 mg/ml (0.9 %) sodium chloride solution for infusion or water for injections, to a concentration of 2 mg/ml.
After reconstitution, Doxorubicin can be administered as intravenous infusion after dilution in the concentration range of 0.05 mg/ml to 0.5 mg/ml in 9 mg/ml (0.9 %) sodium chloride solution for infusion or in 50 mg/ml (5 %) glucose solution for infusion using non-PVC infusion bags.

Personnel should be trained in good technique for handling cytotoxic drugs. Pregnant staff should be excluded from working with this drug. Personnel handling this, and all cytotoxic drugs, should wear protective clothing: goggles, gowns and disposable gloves and masks.

If Doxorubicin comes in contact with skin or mucous membranes, the exposed area should be thoroughly washed with soap and water. If the substance gets into the eyes, rinse with water or sterile physiological saline, whereupon an eye specialist should be consulted.

After use, vials and injection materials, including gloves**,** should be destroyed according to the rules for cytostatics. The vial is for single use only and any unused contents should be discarded. Any unused product or waste material should be disposed of in accordance with local requirements.

Inactivation of spilled or leaked drug can be obtained with 1% sodium hypochlorite solution or most simply with phosphate buffer (pH > 8) until solution is colourless. All cleaning materials should be disposed of as indicated previously.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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