SUMMARY OF PRODUCT CHARACTERISTICS

Doxorubicin Teva

Concentrate for solution for infusion
For I.V. infusion

1. NAME OF THE MEDICINAL PRODUCT

Doxorubicin Teva

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of Doxorubicin Teva contains 2 mg doxorubicin hydrochloride.
5 ml of Doxorubicin Teva contains 10 mg doxorubicin hydrochloride.
10 ml of Doxorubicin Teva contains 20 mg doxorubicin hydrochloride.
25 ml of Doxorubicin Teva contains 50 mg doxorubicin hydrochloride.
100 ml of Doxorubicin Teva contains 200 mg doxorubicin hydrochloride.

Excipients with known effect
Each ml of Doxorubicin Teva contains 3.54 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, red solution. pH = 2.7-3.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Doxorubicin Teva is indicated for producing regression in disseminated neoplastic conditions such as: acute lymphoblastic leukaemia, acute myeloblastic leukaemia, Wilms` tumour, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, lymphomas of both Hodgkin's and non-Hodgkin's types, bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types, and gastric carcinoma.

4.2 Posology and method of administration

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

Doxorubicin hydrochloride 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 assessed 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 measuring renal function (see section 4.4).

Analysis of left ventricular ejection fraction (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).

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 minimizes 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 a continuous infusion for up to 96 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.

Doxorubicin 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). The dosage schedule of doxorubicin administration may vary according to indication (solid tumours or acute leukaemia) 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, patients treated previously 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 populations

Immunosuppressed patients
The dose should be reduced in the 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
> 85 µmol/L	Stop treatment

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

Patients with risk of cardiac impairment
Patients with an increased risk of 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 not related to bone marrow involvement of the disease
The dosages may be reduced in patients with a history of treatment with myelosuppressive agents. Their bone marrow reserve may be insufficient.

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 specialist literature.

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.

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

4.3 Contraindications

Hypersensitivity to the active substance, other anthracyclines or anthracenediones or to any of the excipients listed in section 6.1.

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 maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones (see section 4.4)
- breast-feeding.

Contraindications for intravesical administration
- invasive tumours that have penetrated the bladder (beyond T1)
- 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.

Patients should recover from the acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with doxorubicin.

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)
- inspection of the oral cavity and pharynx for mucosal changes
- blood tests: haematocrit, platelets, differential white cell count, SGPT, SGOT, LDH, bilirubin, uric acid.

The patient should be informed that the urine might be reddish after administration.

Nausea, vomiting and mucositis are often extremely severe and should be prevented and if necessary treated appropriately.

Cardiac function
Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.

Early (i.e. acute) events: Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity and are generally not a consideration for discontinuation of doxorubicin treatment. 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. 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.

Late (i.e. delayed) events: Delayed cardiotoxicity usually develops late in the course of therapy with doxorubicin or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment, have also been reported. Delayed cardiomyopathy is manifested by reduced LVEF 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. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

Cardiac function should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

The probability of developing CHF, estimated around 1% to 2% at a cumulative dose of 300 mg/m^2 slowly increases up to the total cumulative dose of 450-550 mg/m^2. Thereafter, the risk of developing CHF increases steeply and it is recommended not to exceed a maximum cumulative dose of 550 mg/m^2.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones and concomitant use of drugs with the ability to suppress cardiac contractility, or of cardiotoxic substances (e.g., trastuzumab) and age over 70 years. Anthracyclines, including doxorubicin, should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see section 4.5). 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 reported half-life of trastuzumab is variable. This substance may persist in the circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Cardiac function must be carefully monitored in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.

Children and adolescents are at an increased risk for developing delayed cardiotoxicity following doxorubicin administration. Females may be at greater risk than males. Follow-up cardiac evaluations are recommended periodically to monitor for this effect.

It is probable that the toxicity of doxorubicin and other anthracyclines or anthracenediones is additive.

Haematologic toxicity
Doxorubicin may produce myelosuppression (see section 4.8). 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 therapy with doxorubicin is initiated.

Haematologic profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leucopenia and/or

granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopenia and neutropenia generally reach the nadir between days 10 and 14 after drug administration; the WBC/neutrophil counts return to normal values in most cases by day 21. Thrombocytopenia and anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

Secondary leukaemia
Secondary leukaemia with or without a preleukaemic phase, has been reported in patients treated with anthracyclines. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs or when doses of the anthracyclines have been escalated. These leukaemias can have a 1 to 3 year latency period.

Gastrointestinal disorders
Doxorubicin induces nausea and vomiting. Mucositis/stomatitis usually appears early after initiation of treatment, which, if severe, may progress within a few days to mucosal ulcerations. Most patients recover from this in the third week of therapy.
An antiemetic prophylaxis is recommended.
Note: Doxorubicin should not be used in the presence of inflammations, ulcerations or diarrhoea.

Liver function
The major route of elimination of doxorubicin is the hepatobiliary system. Serum total bilirubin should be evaluated before and during treatment with doxorubicin. Patients with elevated bilirubin may experience slower clearance of the drug with an increase in overall toxicity. Lower doses are recommended in these patients (see section 4.2). Patients with severe hepatic impairment should not receive doxorubicin (see section 4.3).

Tumour-lysis syndrome
Doxorubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells (tumour-lysis syndrome) in case of high tumour burden. In these circumstances blood uric acid levels, potassium, calcium phosphate and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumour lysis syndrome.

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

Combination with other anticancer chemotherapies
Doxorubicin hydrochloride may potentiate the toxicity of other anticancer chemotherapies (see section 4.5). Exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhanced hepatotoxicity of 6-mercaptopurine have been reported. Radiation-induced toxicities (myocardium, mucosa, skin and liver) have also been reported.
As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena including pulmonary embolism (in some cases fatal) have been coincidentally reported with the use of doxorubicin (see section 4.8).

Carcinogenesis, mutagenesis and impairment of fertility
Doxorubicin was genotoxic and mutagenic in *in vitro* and *in vivo* tests. Doxorubicin may cause infertility during the period of drug administration (see sections 4.6 and 5.3).

Injection site reaction
Injection into a small vein or repeated injections into the same vein can result in phlebosclerosis. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see section 4.2).

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, debridement 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.

Vaccines
Vaccines are not recommended (see section 4.5).
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving doxorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. During treatment with doxorubicin hydrochloride patients should avoid contact with recently polio vaccinated persons.

Intravesical administration
Intravesical administration of doxorubicin may cause symptoms of chemical cystitis (i.e., dysuria, frequent urinary, 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).

Excipients
Sodium
1 vial of 5 ml of Doxorubicin Teva contains 18 mg sodium, equivalent to 0.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
1 vial of 10 ml of Doxorubicin Teva contains 35 mg sodium, equivalent to 1.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
1 vial of 25 ml of Doxorubicin Teva contains 89 mg sodium, equivalent to 4.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
1 vial of 100 ml of Doxorubicin Teva contains 354 mg sodium, equivalent to 17.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Doxorubicin is a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (e.g., verapamil), resulting in increased concentration and clinical effect of doxorubicin. Conversely, inducers of CYP3A4 (e.g., rifampicin, phenobarbital, phenytoin, St. John's Wort) and of P-gp may decrease plasma levels of doxorubicin and may thus lead to a decrease in efficacy.

Doxorubicin hydrochloride used in combination with cyclosporin might require dose-adjustment. At concomitant administration of cyclosporin, 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. Cyclosporin inhibits, similar to

verapamil, both CYP3A4 and P-glycoprotein, which might explain the interaction and resulting increase in adverse effects. Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and prolonged haematologic toxicity than that observed with doxorubicin alone. Coma and seizures have also been described with concomitant administration of cyclosporine and doxorubicin.

Cimetidine has also been shown to reduce the plasma clearance and increase the AUC of doxorubicin.

Doxorubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastrointestinal effects (see section 4.4). The use of doxorubicin in combination chemotherapy with other potentially cardiotoxic drugs (e.g., 5-fluorouracil, cyclophosphamide or paclitaxel), as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), require monitoring of cardiac function throughout treatment.

Paclitaxel can cause increased plasma-concentrations of doxorubicin and/or its metabolites when given prior to doxorubicin. Certain data indicate that a smaller increase is observed when doxorubicin is administered prior to paclitaxel.

The use of trastuzumab in combination with anthracyclines (such as doxorubicin) is associated with a high cardiotoxic risk. . Trastuzumab and anthracyclines should currently not be used in combination, except for well controlled clinical studies with monitoring of cardiac function (see section 4.4).

(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 hematopoietic 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). Necroses of the large intestine with massive haemorrhage and severe infections have been reported in combination therapies with cytarabine.

Doxorubicin hepatotoxicity may be enhanced by other hepatotoxic treatment modalities (e.g., 6-mercaptopurine).

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.

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 should 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 section 6.2 for more details.

In a clinical study increase in doxorubicin AUC (21-47%) and no increase was observed when given with sorafenib 400 mg twice daily. The clinical significance of these findings is unknown.

4.6 Fertility, pregnancy and lactation

Fertility
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.

Men being treated with doxorubicin are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation (or cryo-preservation) of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with doxorubicin.
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.

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.
Women should not become pregnant during and up to 6 months after treatment.

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: haematuria, vesical and urethral irritation, stranguria and pollakisuria. These reactions are usually of moderate severity and of short duration.

Intravesical administration of doxorubicin may sometimes cause haemorrhagic 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 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Infections and infestations

Very common:	Infection.
Common:	Sepsis/septicaemia.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon:	Acute lymphocytic leukaemia. Acute myeloid 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 (see section 4.4).

Blood and lymphatic system disorders

Very common:	Myelosuppression including leukopenia, neutropenia, thrombocytopenia, anaemia.

Myelosuppression is one of the dose-limiting side-effects and may be serious. It manifests mainly in the decrease of the leukocyte count. Leukopenia 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 a 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 days in most cases. If appearing, thrombocytopenia or anaemia occurs in the same period, but is usually less severe. (see section 4.4).

Immune system disorders

Rare:	Anaphylactic reactions.

Endocrine disorders

Very rare:	Hot flashes.

Metabolism and nutrition disorders

Very common:	Decreased appetite.
Very rare:	Hyperuricaemia.

Eye disorders

Common:	Conjunctivitis.
Not known:	Keratitis, increased lachrymation.

Cardiac disorders

Very common:	Cardiotoxicity.
Common:	Life-threatening congestive (dilatative) cardiomyopathy (after cumulative dose of 550 mg/m²). Sinus tachycardia, ventricular tachycardia, tachyarrhythmia, supraventricular and ventricular extrasystoles, bradycardia, arrhythmia. Asymptomatic reduction of the left ventricular ejection fraction.
Very rare:	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. Atrioventricular block, bundle branch block.

Doxorubicin is cardiotoxic. The risk that the cardiotoxic side-effects become manifest is elevated during and after radiation therapy of the mediastinal region, after pre-treatment with potentially cardiotoxic agents (e.g., anthracyclines, cyclophosphamide), and in elderly patients (over 70 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 signs of left ventricular failure within few months of the termination of 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).

Vascular disorders

Common:	Haemorrhage.
Uncommon:	Thromboembolism.
Not known:	Shock.
	Thrombophlebitis.
	Phlebitis.

Respiratory, thoracic and mediastinal disorders

Not known:	Bronchospasm.

Gastrointestinal disorders

Very common:	Gastrointestinal disturbance.
	Diarrhoea.
	Nausea and vomiting.
	Mucositis, stomatitis, oesophagitis, colitis.
Common:	Abdominal pain.
Uncommon:	Gastrointestinal haemorrhage.
	Necrosis of the large intestine with massive haemorrhage and severe infections in combination therapies with cytarabine.
Very rare:	Gastric erosions/ulcers.
	Ulceration of the mucous membranes (mouth, pharynx, oesophagus, gastrointestinal tract).
	Hyperpigmentation of the oral mucous membrane.

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, when no prophylactic medication is provided (see section 4.4).

Hepatobiliary disorders

Not known:	Hepatotoxicity (sometimes progressing to cirrhosis).
	Transient increase of liver enzymes.

Skin and subcutaneous tissue disorders

Very common:	Alopecia (dose-dependent and in most cases reversible).

	Reddening.
	Photosensitization.
	Palmar-plantar erythrodysaesthesia syndrome.
Common:	Local hypersensitivity reactions in the field of radiation ("radiation recall reaction").
	Pruritus.
	Urticaria.
	Rash (exanthema).
	Hyperpigmentation of skin and nails.
Rare:	Onycholysis.
	Extravasation (may lead to severe cellulitis, vesication, thrombophlebitis, lymphangitis, and local tissue necrosis).
Very rare:	Acral erythemas.
	Blistering.
Not known:	Actinic keratosis

Musculoskeletal and connective tissue disorders

Not known:	Arthralgia.

Renal and urinary disorders

Very common:	Red coloration to the urine.
Common:	Dysuria.
	Chemical cystitis following intravesical administration (with dysuric complaints such as vesical irritation, urethral irritation, dysuria, stranguria, pollakisuria, haematuria, vesicular spasms, hemorrhagic cystitis).
Very rare:	Acute renal failure (isolated cases).
	Hyperuricaemia and subsequent uric acid nephropathy as a consequence of massive tumour lysis.

Reproductive system and breast disorder

Very rare:	Amenorrhoea.
	Oligospermia.
	Azoospermia.

General disorders and administration site conditions

Very common:	Pyrexia.
	Asthenia.
	Chills.
Uncommon:	Dehydration.
Rare:	Dizziness.
	Injection site reactions (local erythematous reactions along the vein, pain, phlebitis, phlebosclerosis).
Not known:	Malaise.

Investigations

Very common:	Ejection fraction decreased, ECG abnormal, transaminases abnormal, weight increased (reported in patients with early breast cancer receiving doxorubicin-containing adjuvant therapy (NSABP B-15 trial)).

Surgical and medical procedures

Not known:	Radiation damage (skin, lungs, oesophagus, gastrointestinal mucosa, heart) that is already healing may reappear following doxorubicin administration.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

4.9 Overdose

Acute overdosage of doxorubicin may lead to myelosuppression (particularly leucopenia and thrombocytopenia), generally 10- 14 days following overdose, gastrointestinal toxic effects (particularly mucositis) and acute cardiac alterations, which may occur within 24 hours. Treatment includes intravenous antibiotics, transfusion of granulocytes and thrombocytes and treatment of the gastrointestinal symptoms and heart effects. Moving the patient to a sterile room and the use of a haemopoietic growth factor should be considered.

Single doses of 250 mg and 500 mg of doxorubicin have proved fatal.

Chronic overdosage, with a cumulative dose exceeding 550 mg/m^2 increases the risk for cardiomyopathy and may lead to heart failure, which should be treated along conventional lines. Delayed cardiac failure may occur up to six months after the overdosage.

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.

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 function results in a slower elimination of the substance.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid or sodium hydroxide for pH adjustment
Water for injections

6.2 Incompatibilities

Doxorubicin must not be mixed with heparin, as this will result in precipitation. Until detailed compatibility information about miscibility is available, doxorubicin should not be mixed with other medicinal products than those mentioned under section 6.6.

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

6.3 Shelf life

Vial before opening
The expiry date of the product is indicated on the packaging materials.

After first opening
Use immediately after first opening.

After dilution
Chemical and physical in-use stability after dilution to a concentration of 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 has been demonstrated for 7 days when stored protected from light at room temperature (15-25˚C) and at 2-8˚C. After dilution to the concentration of 0.05 mg/ml, the diluted solution should be used immediately.

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 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2-8°C).
Do not freeze.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Doxorubicin Teva concentrate for solution for infusion is supplied in vials of 5 ml (10 mg), 10 ml (20 mg), 25 ml (50 mg) or 100 ml (200 mg) containing a red, clear, sterile solution.

Primary packaging material: Vials are of colourless glass type I (Ph.Eur.), with a chlorobutyl rubber stopper with an inert fluoropolymer (PTFE) coating on the inner side and with an aluminium seal covered with a coloured polypropylene disc.

Trade package quantities: Boxes with one vial of 5, 10, 25 or 100 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Doxorubicin can also be administered as intravenous infusion diluted 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 well trained 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, bottles and injection materials, including gloves, should be destroyed according to the rules for cytostatics.
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 destained. All cleaning materials should be disposed of as indicated previously.

7. LICENCE HOLDER AND MANUFACTURER

Teva Israel Ltd.,
124 Dvora HaNevi'a St., Tel Aviv 6944020, Israel.

8. REGISTRATION NUMBER:

061.78.27503

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