SUMMARY OF THE CHARACTERISTICS OF THE MEDICINAL PRODUCT

1. NAME OF THE MEDICINAL PRODUCT

Doxorubicin Ebewe 2 mg/ml – vials

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml concentrate for solution for infusion contains 2 mg doxorubicin hydrochloride.

Other excipient with known effect: 1 ml contains 9 mg sodium chloride

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear red solution
pH value: 2.5–4

4. CLINICAL INFORMATION

4.1 Therapeutic indications

Doxorubicin is used in adults, adolescents and children.

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

Doxorubicin is often used in dosage regimens of combination chemotherapy with other cytostatic agents.

4.2 Posology and method of administration

Strictly for intravenous and intravesical use.
Vials should be at room temperature before being punctured with a needle.
Doxorubicin may only be administered under the supervision of a qualified physician experienced in administering cytostatic therapy. Patients must furthermore be carefully and frequently monitored during treatment.

The risks and benefits for each patient must be weighed before each dose due to the risk of cardiomyopathy, which is frequently fatal.

Estimation of liver function by conventional tests such as determination of AST, ALT, ALP and bilirubin as well as renal function is recommended prior to the start of treatment (see Section 4.4).

LVEF should be determined by ultrasound or cardiac scintigraphy to evaluate the patient's cardiac status. This examination should be performed prior to the start of treatment and after each cumulative dose of approximately 100 mg/m^2 (see Section 4.4).

Intravenous (IV) administration of doxorubicin must be undertaken with great care, and it is advisable to administer the medicinal product through infusion tubing with free-flowing IV saline solution or 5% glucose solution within 3–5 minutes. This method minimises the risk of developing thrombosis and perivenous extravasation, which may result in severe cellulitis, blister formation and tissue necrosis. Doxorubicin may be administered intravenously within minutes as a bolus, for up to an hour as a short-term infusion or for up to 24 hours as a continuous infusion. Direct intravenous injection is not recommended due to the risk of extravasation, which may even occur in the presence of a suitable return of blood by needle aspiration.

Doxorubicin must NOT be administered via the intramuscular, subcutaneous, oral or intrathecal routes.

Intravenous administration:
The dose is usually calculated according to the body surface area (mg/m^2). The dosage regimen for the administration of doxorubicin may vary depending on the indication (solid tumours or acute leukaemia) and on its use in specific treatment regimens (as a single active substance or in combination with other cytostatic agents or as part of multidisciplinary procedures, which include a combination of chemotherapy and surgical procedures, as well as radiotherapy and hormonal treatment).

Monotherapy:
The recommended dose is 60–75 mg/m^2 body surface area by IV as a single dose or in divided doses on 2–3 consecutive days, administered intravenously at intervals of 21 days. The dosage regimen and dosage may be adjusted according to the protocol. Please refer to current protocols for precise dosage information.

Combination treatment:
If doxorubicin is used in combination with other cytostatic agents, the dosage should be reduced to 30–60 mg/m^2 every 3 to 4 weeks.

Maximum cumulative dose:
The maximum total dose of 450–550 mg/m^2 body surface area must not be exceeded (including administration with related medicinal products such as daunorubicin).

The maximum total dose of 400 mg/m^2 body surface area must not be exceeded in patients with concomitant heart disease who undergo radiation therapy of the mediastinum and/or

heart, or who have had prior treatment with alkylating substances and high-risk patients (e.g. patients with arterial hypertension for more than 5 years; patients with prior coronary, valvular or myocardial heart disease or patients over 70 years of age), and the cardiac function of these patients must be monitored (see Section 4.4).

Special populations:

Immunosuppressed patients:
The dose must be reduced in immunosuppressed patients; an alternative dosage is 15–20 mg/m^2 body surface area per week.

Patients with impaired hepatic function:
The dose should be reduced in accordance with the following table in patients with impaired hepatic function:

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 hepatic impairment (see Section 4.3).

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

Patients with risk of cardiac failure:
Treatment with a 24-hour-long continuous infusion of a single dose instead of an injection should be considered in patients with an increased risk of cardiac toxicity. This may reduce the frequency of occurrence of cardiac toxicity without reduction in therapeutic efficacy. The ejection fraction should be measured before each course of treatment in these patients.

Patients with limited bone marrow reserve:
Dosages may be reduced in patients with a history of treatment with myelosuppressive agents, since their bone marrow reserve can be inadequate.

Obese patients:
It may be necessary to consider a reduced initial dose or a longer dose interval in obese patients (see Section 4.4).

Elderly patients (65 years and over):
Dosages may be reduced in elderly patients.

Paediatric population:
In view of the substantial risk of doxorubicin-induced cardiotoxicity during childhood, certain cumulative maximum doses should be administered, depending on the age of the patient. The maximum cumulative dose in children (under 12 years of age) is usually 300 mg/m^2, while the maximum cumulative dose is fixed at 450 mg/m^2 for adolescents (over 12 years of age). The maximum cumulative dosages in young children are still undecided, but much lower tolerability is assumed.

Dosage should be reduced in children, since they have an increased risk of cardiotoxicity, especially for late-onset disease. Myelotoxicity should be expected, with nadir values at 10 to 14 days after the start of treatment. Please refer to current treatment protocols and specialist literature.

Intravesical administration:
Doxorubicin may be administered by intravesical instillation for the treatment of superficial bladder cancer and to prevent a recurrence following transurethral resection (TUR). The recommended dose for the intravesical treatment of superficial bladder carcinoma is 30–50 mg in 25–50 ml physiological saline solution per instillation. The optimum concentration is approximately 1 mg/ml. The solution should remain in the bladder for 1–2 hours. During this period, the patient must be turned by 90° every 15 minutes. The patient should be instructed not to drink anything for a period of 12 hours prior to instillation in order to prevent any undesired dilution of urine (this should reduce urine production to approximately 50 ml/h). Instillation may be repeated at an interval of 1 week to 1 month depending on whether treatment is therapeutic or prophylactic.

4.3 Contraindications

Hypersensitivity to doxorubicin, other anthracyclines or anthracenediones or to any of the excipients listed in Section 6.1.
Treatment with doxorubicin during pregnancy and while breastfeeding is contraindicated (see Section 4.6).

Contraindications to intravenous administration
Doxorubicin is contraindicated:
- in patients with marked, persistent myelosuppression and/or severe stomatitis, induced by previous cytotoxic treatment and/or radiation therapy (including patients with a high risk of haemorrhage)
- in patients with a history of cardiac disease (unstable angina pectoris, progressive heart failure, severe cardiac arrhythmias and conduction disorders, acute inflammatory heart diseases, myocardial infarction during the last 6 months, cardiomyopathy)
- in patients with severe liver damage (see Section 4.2).
- in patients who have already been treated with anthracyclines (e.g. epirubicin, idarubicin or daunorubicin) up to the respective maximum cumulative dose
- in acute infections
- in haemorrhagic diathesis
- in inflammation of oral mucous membranes

Contraindications to intravenous administration:
- invasive tumours which have penetrated the bladder (over and above T_1)
- urinary tract infections and bladder inflammation
- problems with catheterisation
- haematuria

4.4 Special warnings and precautions for use

General warnings
Doxorubicin may only be administered under the supervision of a qualified physician experienced in administering cytostatic therapy. Patients must furthermore be carefully and frequently monitored during treatment.

Patients should recover from acute toxic effects of previous cytotoxic therapy (such as stomatitis, neutropenia, thrombocytopenia and generalised infections) before treatment with doxorubicin is initiated.

Therapy with doxorubicin requires careful observation of the patient and laboratory values, especially in elderly patients, in patients with a history of heart disease or bone marrow suppression and in patients who have been previously administered anthracyclines or radiation therapy to the mediastinum.

The following tests are recommended for monitoring prior to or during treatment with doxorubicin (how often these examinations are performed depends on the general health of the patient, the dose and intake of concomitant medication):

- chest x-rays and ECG,
- regular monitoring of cardiac function (LVEF by e.g. ECG, UKG (*Ultraschallkardiographie* [echocardiography]) and MUGA scan),
- daily inspection of the oral cavity and pharynx for changes in the mucous membranes,
- blood tests: haematocrit, platelets, differential white blood count, SGPT, SGOT, LDH, bilirubin, uric acid.

Hepatic function should be monitored during and after treatment in patients with a history of hepatitis B or C (if necessary, antibody test), since reactivation of the disease cannot be excluded.

Appropriate measures must be taken to check for any systemic infections prior to the start of treatment. Doxorubicin is only to be administered by safe intravascular injection, since paravenous injection leads to local necrosis and thrombophlebitis. Doxorubicin must not be administered by intramuscular, subcutaneous, oral or intrathecal routes.

The systemic clearance of doxorubicin is reduced in obese patients (i.e. >130% ideal body weight) (see Section 4.2).

The patient should be informed that urine may be reddish in colour after administration.

Nausea, vomiting and mucositis are often extremely severe and must be appropriately treated.

Cardiotoxicity
The risk of myocardial toxicity may be increased after simultaneous or prior mediastinal/pericardial radiation therapy or after treatment with other potentially cardiotoxic substances, in patients over age 70 or under 15 years of age, as well as in patients with a special disease-related clinical condition, such as anaemia, leukaemic pericarditis and/or myocarditis.

Cardiac function should be closely examined prior to the start of treatment and monitored carefully during treatment to reduce the risk of cardiotoxicity, as described for other anthracycline compounds. A history of cardiac disease and prior therapy with anthracyclines in high cumulative doses or with other potentially cardiotoxic agents are co-factors for an increased risk of doxorubicin-induced cardiotoxicity.

If the maximum total cumulative dose is exceeded (550 mg/m² BSA in adults, 400 mg/m² BSA in cases with a history of previous radiation therapy of the thorax or during concomitant therapy), the rate of anthracycline-induced cardiomyopathy increases rapidly even in the absence of risk factors. However, cardiotoxicity has been observed at much lower doses in isolated cases. Patients have, for instance, an approximately 5% risk of developing serious heart failure after a cumulative total dose of 550 mg/m² BSA.

The cumulative dose must be considered if the medicinal product is used in children who tolerate only low total lifetime doses and undergo additional radiation therapy. Young age at the start of therapy and aggressive concomitant therapy is associated with a particularly high risk of developing late-onset, life-threatening cardiotoxicity with ventricular dysfunction, heart failure and/or arrhythmias. As compared to boys, girls seem to be particularly predisposed to the development of delayed cardiotoxicity after therapy with doxorubicin.

Special caution is also indicated in children younger than 2 years of age and in patients with a history of previous cardiological treatment (coronary heart disease, heart failure), as well as with chronological reference to hyperthermic therapy.

Female patients are at higher risk than males. Cardiological follow-up examinations are recommended to monitor this effect. The risk-benefit ratio of doxorubicin therapy should therefore be weighed in such patients prior to the start of treatment.
Women who have been treated with doxorubicin in the past (up to 20 years prior) may also develop cardiac symptoms during pregnancy, even if they had no signs of side effects on the heart. Cases of congestive heart failure and pulmonary oedema have been reported. Women who have been treated with doxorubicin in the past and become pregnant must be monitored for cardiac side effects. See also Section 4.8.

Cardiotoxicity may occur in two different forms:

The **immediate type** is dose-dependent and is characterised by non-specific ECG changes (ST-segment depression, sinus tachycardia and supraventricular and ventricular extrasystoles). Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle branch blocks have also been reported. Generally, these symptoms do not herald late-onset cardiotoxicity and are clinically not significant. Therapy may be continued in most cases.
However, life-threatening arrhythmias may occur during or several hours after administration of doxorubicin; acute left ventricular failure, pericarditis or fatal pericarditis-myocarditis-syndrome have been reported in isolated cases.

The **late type** is dose-dependent and represents cumulative organ toxicity occurring as cardiomyopathy. This reaction usually occurs later during the course of treatment with doxorubicin or within 2–3 months after the end of treatment; however, cases have been observed even later (several months to years after the end of therapy).
It most commonly manifests as left ventricular failure and/or signs or symptoms of congestive heart failure such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion and tachycardia. Subacute effects such as pericarditis/myocarditis have also been observed. Life-threatening heart failure is the most severe form of anthracycline-induced cardiomyopathy and represents cumulative dose-limiting toxicity of the substance.

As long as there is no reliable method for the prediction of acute heart failure, anthracycline-induced cardiomyopathy will continue to be associated with sustained reduction in QRS voltage, the increase in the systolic interval (PEP/LVEF) beyond normal limits and decrease in left ventricular ejection fraction (LVEF) as compared to pre-treatment baseline values. Electrocardiograms, echocardiography and a MUGA scan should be performed and the left ventricular ejection fraction estimated before and during treatment (after each cumulative dose of approximately 100 mg/m^2 and in the event of clinical signs of heart failure).
In patients with normal initial LVEF, an absolute decrease of ≥10% or a decrease below 50% is considered evidence of cardiac impairment is considered a rule of thumb. Continuation of treatment with doxorubicin must be evaluated carefully in these cases.

The early clinical diagnosis of doxorubicin-induced myocardial damage appears to be important for the benefit of pharmacological treatment. Treatment with digitalis, diuretics, as well as sodium restriction and bed rest are indicated.

The probability of heart failure, estimated to be 1–2% with a cumulative dose of 300 mg/m², increases gradually up to a total cumulative dose of 450–550 mg/m². The probability of heart failure increases steeply with still higher dosages. Exceeding the maximum cumulative dose of 550 mg/m² is therefore not recommended.

The risk factors of cardiotoxicity include:

- active or latent cardiovascular diseases
- prior or simultaneous radiation therapy of the mediastinal or pericardial area
- prior treatment with other anthracyclines or anthracenediones
- concomitant administration of substances that can suppress heart muscle contractions
- concomitant administration of cardiotoxic substances (e.g. trastuzumab)
- being over 70 years of age

There is an increased risk of developing cardiotoxicity in patients being administered anthracyclines with other cardiotoxic substances after treatment has ended (especially those with long half-lives, such as trastuzumab). Since the half-life of trastuzumab is approximately 28–38 days, trastuzumab can circulate in the blood for up to 27 weeks after treatment has ended. If possible, physicians should refrain from anthracycline-based therapy after discontinuation of trastuzumab for up to 27 weeks. If anthracyclines have been previously administered, the patient's cardiac function should be carefully monitored.

A total cumulative dose of 400 mg/m² should not be exceeded in adults under these circumstances. Cardiac function must be monitored carefully in patients who receive high cumulative doses and in those with risk factors.
However, doxorubicin may also trigger cardiotoxicity at low cumulative doses and even if no risk factors are foreseeable.

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

It has been reported that acute severe arrhythmias may occur during or within a few hours after administration of doxorubicin.

Myelosuppression
Doxorubicin, like other cytotoxic substances, may cause myelosuppression.

Haematological values should be examined before and during each treatment cycle, including a differential count of white blood cells. Dose-dependent reversible leukopenia and/or neutropenia are the most important manifestations of doxorubicin haematotoxicity and the most frequent dose-limiting toxicity of this substance. Doxorubicin-induced bone marrow suppression primarily involving leukocytes requires comprehensive haematological monitoring, as severe myelosuppression may lead to superinfections and bleeding.

Leukopenia and neutropenia are generally more severe with high-dose regimens, with the nadir occurring between the 10th and 14th days after administration in most cases; these are usually transient – the number of leukocytes/neutrophils return to normal by the 21st day in most cases. It should be decided whether or not to begin or continue treatment if the polynuclear granulocyte count is less than 2000/mm³. This figure may be adjusted in the treatment of acute leukaemia depending on the circumstances.
Thrombocytopenia and anaemia may also occur. The clinical sequelae of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.
Doxorubicin must not be used if severe myelosuppression is present; a dose reduction or delay in administration is then necessary.
Care must be taken to ensure that a severe infection and/or episode of haemorrhaging can be treated quickly and effectively. Existing infections should be treated before therapy with doxorubicin is initiated.

The occurrence of secondary myeloid leukaemia with or without a pre-leukaemic phase has been observed in patients treated with anthracyclines (including doxorubicin). Secondary leukaemia occurs more frequently if anthracyclines are administered in combination with DNA-damaging antineoplastic agents (e.g. alkylating agents, platinum derivatives) or with radiation therapy in patients who were previously treated with high doses of cytotoxic agents or high doses of anthracyclines. This type of leukaemia may have a latent period of 1–3 years. Regular haematological examination is required.

Gastrointestinal disorders
Doxorubicin causes nausea. Mucositis or stomatitis usually occur soon after the start of treatment and may lead to mucosal ulcers within a few days in severe cases. Most patients recover from these side effects during the third week of treatment.

Note: Doxorubicin should not be used in cases of inflammation, ulcerations and diarrhoea.

Secondary oral neoplasms
Very rare cases of secondary oral cavity carcinoma have been reported in patients with long-term doxorubicin exposure (longer than a year) or who have received a total doxorubicin dose of more than 720 mg/m². Cases of secondary oral cavity carcinoma were diagnosed both during treatment with doxorubicin and for up to 6 years after administration of the last dose. Patients must be examined at regular intervals for oral ulcerations or other oral symptoms which may indicate the presence of a secondary oral cavity carcinoma.

Skin reactions at the injection site (extravasation)
Phlebosclerosis may occur due to injection into a small vein or by repeated puncture of the same vein. Precise compliance with the recommended methods of administration reduces the risk of phlebitis/thrombophlebitis at the injection site (see Section 4.2).

Extravasation of doxorubicin during intravenous injection may cause local pain, severe tissue damage (blister formation, severe cellulitis), necrosis, lymphangitis and thrombophlebitis.
A feeling of stabbing or burning around the infusion needle indicates extravasation. The infusion or injection must be stopped immediately if extravasation occurs. The cannula should initially be left in place and removed after brief aspiration. Administration must be restarted in another blood vessel.

Intravenous infusion of dexrazoxane is recommended no later than 6 hours after extravasation (see the SmPC for dexrazoxane for dosage and further information). In cases where dexrazoxane is contraindicated, local application of 99% DMSO is recommended over an area twice as large as the affected area (4 drops over 10 cm² skin surface area), and should be repeated three times daily over a period of at least 14 days. Debridement should be considered if necessary. Cooling of the area, e.g. to reduce pain, and application of DMSO should be performed sequentially (vasoconstriction vs. vasodilatation) in view of the conflicting mechanism. Other measures have been controversially described in the literature and are of no clear value.

Liver function tests
Doxorubicin is mainly eliminated via the hepatobiliary system. The elimination of the medicinal product may therefore be prolonged with resultant general toxicity if liver function is impaired or if biliary secretion is inhibited. Liver function tests, including conventional tests such as estimation of AST, ALT, ALP and bilirubin, are recommended before and during treatment since a dose adjustment may be necessary (see Section 4.2). Patients with severe hepatic impairment should not be treated with doxorubicin (see Section 4.3). Severe, occasionally fatal, hepatotoxicity has been reported in patients who have undergone previous mediastinal radiation therapy.

Test for uric acid in serum
Serum uric acid levels may increase during therapy. Anti-hyperuricaemic therapy should be initiated if hyperuricaemia is present.

Uric acid levels in the blood should be monitored; sufficient fluid intake (with a daily minimum of 3 l/m²) must be ensured. A xanthinoxidase inhibitor (allopurinol) may be administered if necessary.

Dose reductions may be necessary in patients with severely impaired renal function (see Section 4.2).

Radiation therapy
Special caution is mandatory in patients who have previously received radiation therapy, are currently receiving radiation therapy, or plan to receive radiation therapy. These patients carry a special risk of local reactions in the radiation field (recall phenomenon) when doxorubicin is used. Severe, occasionally fatal, hepatotoxicity has been reported in this context. Prior radiation therapy of the mediastinum increases cardiotoxicity due to doxorubicin. The cumulative dose of 400 mg/m² must not be exceeded in this case in particular.

Carcinogenesis, mutagenesis and impairment of fertility
Doxorubicin was genotoxic and mutagenic in in vitro and in vivo tests.

Doxorubicin may cause infertility in women during the period of administration of the medicinal product. Doxorubicin may cause amenorrhoea. Ovulation and menstruation appear to return after the end of therapy, but premature menopause may occur.

Doxorubicin is mutagenic and may cause chromosomal damage in human sperm. Oligospermia or azoospermia may be permanent; however, it was reported that sperm counts returned to normal in some cases. This may occur several years after the end of therapy. Men undergoing treatment with doxorubicin must use effective contraceptive methods. Men being treated with doxorubicin are advised not to father a child during and for up to 6 months after treatment, and to seek advice on cryopreservation (or cryoconservation) of sperm prior to treatment due to the possibility of irreversible infertility due to therapy with doxorubicin. Women should not become pregnant during and up to 6 months after treatment.

Other
Doxorubicin may potentiate the toxicity of other chemotherapeutic agents for cancer (see Section 4.5). It may worsen cyclophosphamide-induced haemorrhagic cystitis and favour the development of hepatotoxicity due to 6-mercaptopurine. Toxic reactions (myocardium, mucosa, skin and liver) to radiation therapy have also been reported.
Thrombophlebitis and thromboembolic events, including pulmonary embolism (sometimes with a fatal outcome), have been reported in isolated cases.

Tumour lysis syndrome
Treatment with doxorubicin may cause hyperuricaemia due to marked purine catabolism, which usually accompanies the rapid disintegration of neoplastic cells (tumour lysis syndrome). Uric acid, potassium, calcium phosphate and creatinine levels in blood should be checked after initial treatment. Hydration, urine alkalisation and prophylaxis with allopurinol to prevent hyperuricaemia may minimise the risk of possible complications of a tumour lysis syndrome.

Additional warnings and precautions for other forms of administration

Intravesical

Intravesical administration of doxorubicin may give rise to symptoms of chemical cystitis (i.e. dysuria, polyuria, nocturia, bladder symptoms, strangury, haematuria, necrosis of the bladder wall) and bladder contracture.

Special attention is necessary in the case of problems with catheters (i.e. in case of urethral obstruction caused by invasion of the intravesical tumour).

Intravesical administration is contraindicated in tumours which penetrate the bladder (over and above T1).

Intravesical administration should not be attempted in patients with invasive tumours which have penetrated the bladder wall, in urinary tract infections and in inflammatory diseases of the bladder.

Vaccinations
The administration of live vaccines or attenuated live vaccines in patients whose immune system is impaired by chemotherapeutic agents, including doxorubicin, can cause serious or fatal infections. In general, this medicinal product is not recommended in combination with live vaccines.
Dead or deactivated vaccines can be administered; however, the response to such vaccines can be reduced (see Section 4.5).

Important information about a specific excipient of doxorubicin:
One vial of 5/25/50/100 ml concentrate for solution for infusion contains 0.77/3.85/7.7/15.4 mmol (17.7/88.5/177/354 mg) sodium, equivalent to 0.885/4.425/8.85/17.7% of the maximum daily sodium intake through food recommended by the WHO of 2 g.

4.5 Interactions with other medicinal products and other forms of interaction

Concomitant administration of other antineoplastic substances, such as anthracyclines (daunorubicin, epirubicin, idarubicin), cisplatin, cyclophosphamide, cyclosporine, cytarabine, dacarbazine, dactinomycin, 5-fluorouracil, mitomycin C and taxanes may increase the risk of doxorubicin-induced decompensated heart failure. The availability of doxorubicin was significantly changed when administered immediately after a short intravenous infusion of paclitaxel. The concomitant administration of paclitaxel causes reduced clearance of doxorubicin, and more frequent episodes of neutropenia and stomatitis were observed. Available data suggests that this effect is milder if anthracycline is administered before paclitaxel.
Increased cardiotoxicity was also reported after the concomitant intake of cardioactive medicinal products such as calcium antagonists and verapamil (with an increase in the maximum doxorubicin level, prolongation of terminal half-life and an increase in the volume of distribution). Careful monitoring of cardiac function is indicated for all combinations of this type.

The use of trastuzumab in combination with anthracyclines (such as doxorubicin) is associated with a high cardiotoxic risk.
Trastuzumab and anthracyclines should not be used together until further notice except in carefully controlled clinical studies with monitoring of cardiac function. There is an increased risk of developing cardiotoxicity in patients being administered anthracyclines after conclusion of therapy with other cardiotoxic substances, especially those with long half-lives (such as trastuzumab). Since the half-life of trastuzumab is approximately 28–38 days, trastuzumab may still be present in the circulation for up to 27 weeks after discontinuation of treatment. The physician should avoid anthracycline therapy for up to 27 weeks after discontinuation of trastuzumab if possible. The patient’s cardiac function should be carefully monitored in case of prior use of anthracyclines.

Doxorubicin is metabolised via the cytochrome P450 (CYP450) enzyme system and is a substrate of the Pgp transport system. The concomitant administration of inhibitors of CYP450 and/or Pgp could lead to an increase in plasma concentrations of doxorubicin and thus to increased toxicity. Conversely, the concomitant use of CYP450 inducers, such as rifampicin and barbiturates, may result in a decrease in plasma concentrations of doxorubicin and reduced efficacy.

Doxorubicin may require dose adjustment in combination with cyclosporine. Clearance of doxorubicin is reduced by approximately 50% with concomitant administration of cyclosporine. The AUC of doxorubicin and doxorubicinol is increased by 55% and 350% respectively. A reduction in the dose by 40% is recommended with this combination. Similar to verapamil, cyclosporine inhibits both CYP3A4 and P-glycoprotein, which could explain the interaction and the resulting increase in side effects.

Literature reports indicate that the addition of cyclosporins to doxorubicin results in more severe and longer-lasting haematological toxicity than that observed in doxorubicin alone. Coma and seizures were also described with the simultaneous administration of ciclosporin and doxorubicin.

Cytochrome P-450 inhibitors (e.g. cimetidine) likewise reduce plasma clearance and increase the AUC of doxorubicin, possibly through similar mechanisms as suggested for cyclosporine.

An increased incidence of haemorrhagic cystitis has been reported following administration of cyclophosphamide following doxorubicin therapy.
Concomitant use of doxorubicin reduces the absorption of antiepileptics (e.g. carbamazepine, phenytoin, valproate).

Since doxorubicin is rapidly metabolised and is largely eliminated through the biliary tract, the concomitant administration of known hepatotoxic chemotherapeutic agents (e.g. 6-mercaptopurine, methotrexate, streptozocin) could potentially increase the toxicity of the substance due to the decreased hepatic clearance of doxorubicin. The dosage of doxorubicin must be adjusted if concomitant therapy with hepatotoxic medicinal products is urgently required.

Impaired haematopoiesis was observed following the concomitant administration of substances with an effect on bone marrow function (e.g. amidopyrine derivatives, antiretroviral medicinal products, chloramphenicol, phenytoin, sulphonamides). The dosage of doxorubicin must be changed if necessary.

An increased occurrence of neutropenia and thrombocytopenia has been reported with concomitant use of progesterone.

The combination of doxorubicin with amphotericin B should be avoided since it may lead to pronounced nephrotoxicity.

Increased serum doxorubicin levels have been reported with concomitant administration of doxorubicin and ritonavir.
The toxic effects of doxorubicin therapy may be potentiated in combination with other cytostatic agents (e.g. cytarabine, cisplatin, cyclophosphamide). Colonic necrosis with major bleeding and severe infections has been reported in association with combination therapy with cytarabine.

Clozapine may increase the risk and severity of the haematotoxicity of doxorubicin.

Doxorubicin is a strong radiation-sensitising substance (a “radiosensitiser”), and doxorubicin-induced recall phenomena may be life-threatening. Any previous, concomitant or subsequent

radiation therapy may increase the cardiotoxicity or hepatotoxicity of doxorubicin. This also applies to concomitant therapy with cardiotoxic or hepatotoxic medicinal products.

Doxorubicin may lead to exacerbation of haemorrhagic cystitis caused by prior cyclophosphamide therapy.

Doxorubicin may reduce the oral bioavailability of digoxin.

Therapy with doxorubicin may lead to an increase in serum uric acid concentration; dose adjustment of uric acid-lowering medicinal products may therefore be necessary.
Concomitant use of medicinal products which delay the excretion of uric acid (e.g. sulphonamides and certain diuretics) may lead to hyperuricaemia.

Live vaccines must not be used during doxorubicin therapy due to the risk of a generalised disease which may be fatal. The risk is increased in patients who are immunocompromised due to their underlying disease. During treatment with doxorubicin, patients should also avoid contact with persons recently vaccinated against polio (see Section 4.4).

The concomitant administration of heparin and doxorubicin may lead to an increase in the clearance rate of doxorubicin. Doxorubicin binds to heparin and 5-fluorouracil. Precipitation and loss of efficacy of both substances may therefore occur (see Section 6.2).

4.6 Fertility, pregnancy and breastfeeding

Pregnancy:
Doxorubicin must not be administered during pregnancy. In general, cytostatic agents may be administered during pregnancy only when strictly indicated and if the benefit for the mother was weighed against possible damage to the foetus. Doxorubicin has shown embryotoxic, foetotoxic as well as teratogenic effects in animal studies (see Section 5.3).

Men and women must use effective contraceptive methods during and for up to 6 months after treatment (see Section 4.4).

Breastfeeding:
It has been reported that doxorubicin is excreted in human milk. A risk for the breastfed infant cannot be excluded. As doxorubicin is contraindicated during breastfeeding, breastfeeding must be discontinued during treatment with doxorubicin (see Section 4.3).

Fertility:
Doxorubicin may cause amenorrhoea and infertility in women during treatment. Ovulation and menstruation generally return to normal after the end of therapy, but premature menopause has also been reported.

Toxic effects of doxorubicin on male reproductive organs (testicular atrophy, diffuse degeneration of the vas deferens and hypospermia) have been observed in animal studies.

Doxorubicin has been shown to be mutagenic and may induce chromosomal damage in human sperm. Oligospermia or azoospermia may be irreversible. Normalisation of sperm counts has also been reported in some cases, sometimes years after completion of therapy. Men who are treated with doxorubicin must use reliable contraceptive measures.

4.7 Effects on ability to drive and use machinery

No studies have been performed on the effects on the ability to drive and operate machinery. However, nausea and vomiting are common, and patients must be warned before driving vehicles and operating machinery.

4.8 Side effects

Treatment with doxorubicin often causes side effects, and some of these side effects are serious enough to warrant careful monitoring of the patient. The frequency and type of side effects are influenced by the rate of administration and the dosage. Bone marrow suppression is an acute dose-limiting side effect, but it is usually transient.
Clinical sequelae of doxorubicin-induced bone marrow toxicity/haematological toxicity may include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.
Nausea and vomiting, as well as alopecia, are seen in almost all patients.
Extravasation of doxorubicin may cause local pain, severe tissue damage (blister formation, severe cellulitis), necrosis and thrombophlebitis (see Section 4.4).

Side effects reported in conjunction with doxorubicin treatment are listed below according to the MedDRA system organ class and frequency. The evaluation of adverse reactions is based on the following frequencies:
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 (frequency cannot be calculated based on available data).

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Infections and infestations	Infections	Sepsis/ septicaemia	Septic shock			
Benign, malignant and unspecified neoplasms (including cysts and polyps)			Acute lymphocytic leukaemia, acute myeloid leukaemia		Secondary oral neoplasms (see Section 4.4)	
Blood and lymphatic system disorders	Myelosuppression * including leukopenia, neutropenia, febrile neutropenia, pancytopenia, thrombocytopenia, anaemia, tissue hypoxia or tissue death*		Secondary leukaemia			
Immune system disorders				Angioedema of the eyelids and tongue with respiratory impairment	Anaphylaxis	Anaphylactic reaction
Metabolism and nutritional disorders	Anorexia	Dehydration			Hyperuricaemia	Tumour lysis syndrome (see Section 4.4)
Eye disorders		Conjunctivitis				Keratitis, increased lacrimation
Cardiac disorders		Cardiotoxicity**, e.g. life-threatening congestive (dilative) cardiomyopathy (after cumulative			Non-specific ECG changes (ST changes, low voltage, long QT intervals). Isolated cases	

	Very common	Common	Uncommon	Rare	Very rare	Not known
		dose of 550 mg/m²), sinus tachycardia, ventricular tachycardia, tachyarrhythmia, bradycardia, supraventricular and ventricular extrasystoles, arrhythmia; asymptomatic reduction in left ventricular ejection fraction			of life-threatening arrhythmias, acute left ventricular failure, pericarditis, fatal pericarditis/ myocarditis syndrome; atrioventricular block, fascicular block	
Vascular disorders	Thrombophlebitis	Haemorrhage, phlebitis	Thromboembolism	Shock		Hot flushes
Respiratory, thoracic and mediastinal disorders				Respiratory disorders, swelling of the nasal mucosa, tachypnoea and dyspnoea, radiation pneumonitis****		Bronchospasms
Gastrointestinal disorders	Gastrointestinal disorders***, including nausea and vomiting, diarrhoea; mucositis, stomatitis	Oesophagitis, abdominal pain or burning sensation	Gastrointestinal haemorrhage, colitis, erosive gastritis, necrosis of the large intestine with massive haemorrhage and severe infections with the combination of doxorubicin and cytarabine		Gastric erosion, discolouration of the oral mucous membranes	
Hepatobiliary disorders						Hepatotoxicity, transient increase in liver enzymes (see Section 4.4)
Skin and subcutaneous tissue disorders	Alopecia (dose-dependent and reversible in most cases), onycholysis, redness (erythema), photosensitivity, exanthema, local toxicity	Local hypersensitivity reactions in the radiation field (radiation recall reaction), itching (pruritus), hyperpigmentation of skin and nails, urticaria		Extravasation (may lead to severe cellulitis, vesiculation, thrombophlebitis, lymphangitis and local tissue necrosis)	Acral erythema	Actinic keratosis, palmar plantar erythrodysaesthesia
Musculoskeletal, connective tissue and bone disorders					Generalised muscle weakness	Arthralgia
Renal and urinary disorders		After intravesical administration: cystitis with symptoms of dysuria, polyuria, nocturia, stranguria, pollakiuria, haematuria, bladder spasms, necroses, hemorrhagic cystitis				Red discolouration of urine 1-2 days after administration, acute renal failure
Disorders of the reproductive					Amenorrhoea, oligospermia,	

	Very common	Common	Uncommon	Rare	Very rare	Not known
system and mammary glands					azoospermia	
General disorders and administration site complaints	Fever, asthenia, chills	Reactions at sites of administration		Dizziness	General malaise	Phlebosclerosis (see Section 4.4)
Examinations	Asymptomatic LVEF reduction, abnormal ECG, abnormal transminase levels, weight gain[a]					
Surgical and medical interventions						Healed radiation-induced damage (skin, lungs, oesophagus, gastrointestinal mucous membranes, heart) may recur after administration of doxorubicin

[a] In patients with early stage breast cancer who received adjuvant therapy with doxorubicin (NSABP B-15 study)

The described side effects of doxorubicin therapy are usually reversible.

* Myelosuppression is one of the dose-limiting side effects and may be serious. It manifests mostly as a decrease in the leukocyte count. Leukopenia was observed in nearly 75% of patients with adequate bone marrow reserves who were treated every 21 days with a dose of 60 mg/m² BSA. Thrombocytopenia, neutropenia, and anaemia were also reported, but were less common. Superinfections (very common) and haemorrhages were observed equally in conjunction with bone marrow suppression. Myelosuppression usually peaks 10 to 14 days after administration of doxorubicin and decreases in most cases between the 21st and 28th days. Thrombocytopenia or anaemia may occur during the same period but are usually less severe (see Section 4.4).

** Doxorubicin is cardiotoxic. The risk of developing cardiotoxic side effects is increased during and after radiation therapy of the mediastinal-pericardial region, after prior treatment with potentially cardiotoxic agents (e.g. anthracyclines, cyclophosphamide), in patients over the age of 70 or under 15 years, and in patients with a specific disease-related clinical condition (see Section 4.4).

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

**** Radiation-related pneumonitis with fatal complications was observed in a study on systemic combination chemotherapy of doxorubicin with methotrexate and cyclophosphamides. Occurrence of dyspnoea should be primarily seen as a sign of anthracycline-induced cardiomuscular damage.

An isolated case of myasthenia has also been reported.

Reporting suspected side effects
Reporting suspected side effects after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Bundesamt für Sicherheit im Gesundheitswesen [Federal Agency for Safety in Health Care]
Traisengasse 5
1200 VIENNA
AUSTRIA
Fax: +43 (0) 50 555 36207
Website: http://www.basg.gv.at/

4.9 Overdose

Very high single doses cause weakening of cardiac muscle, including stenocardia, angina pectoris and myocardial infarction, within 24 hours; severe myelosuppression (leukopenia and thrombocytopenia in particular) within 10–14 days, and gastrointestinal toxicity (primarily mucositis).
Treatment with doxorubicin must be discontinued in the event of cardiac muscle weakness. General countermeasures may be required in patients with severe myelosuppression, such as blood transfusions, antibiotics and relocation of patients to germ-free rooms.

Doxorubicin cannot be removed by dialysis.
There is no known specific antidote for doxorubicin.

Chronic overdose with a cumulative dose of more than 550 mg/m² increases the risk of cardiomyopathy and may lead to heart failure, which should be treated by conventional means. Delayed heart failure may occur up to 6 months after an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, cytotoxic antibiotics and related substances, anthracyclines and related substances
ATC code: L01DB01

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

The biological activity of doxorubicin is attributed to its DNA-binding properties, which result in the inhibition of the enzyme system crucial for DNA replication and transcription.

Blocking of the cell cycle appears to be at its peak during the S-phase and mitosis, but inhibition has also been observed during other phases of the cell cycle.

5.2 Pharmacokinetic properties

Triphasic elimination of doxorubicin from the plasma occurs after intravenous administration with a terminal half-life of approximately 30 hours. The volume of distribution is about 25 l/kg. The level of protein binding in the plasma is approximately 70%.

The highest medicinal product concentrations are achieved in the lungs, liver, spleen, kidneys, 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. Approximately 5% is recovered in the urine within five days, while 40–50% is excreted in the bile within 7 days. Reduced liver function results in slower elimination of the substance.

5.3 Preclinical safety data

Literature on animal studies shows that doxorubicin affects fertility and is embryo- and foetotoxic as well as teratogenic. Other data shows that doxorubicin is mutagenic.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

Sodium chloride, hydrochloric acid solution for pH adjustment, water for injection

6.2 Incompatibilities

Contact with solutions with an alkaline pH should be avoided, as this would result in hydrolysis of the medicinal product. Doxorubicin should not be mixed with heparin and 5-fluorouracil, as this may result in the formation of precipitates. This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life

Two years.

Solution for infusion after dilution
Chemical and physical stability of the ready-to-use preparation has been demonstrated as follows:

- Concentration 1.0 mg/ml: 28 days at 2–8°C and at room temperature with and without protection from light
- Concentration 0.1 mg/ml: 4 days at 2–8°C and at room temperature with and without protection from light

Remove the solution from the vial immediately before use.
From a microbiological perspective, this infusion solution must be used immediately. If it is not used immediately, the storage times and conditions prior to use are the responsibility of the user, and the storage times at 2–8°C should generally not exceed 24 hours, unless dilution was carried out under controlled and validated aseptic conditions.

For single use only. Dispose of any unused product.

6.4 Special precautions for storage

Store in the refrigerator (2–8°C).
Store in the original packaging in order to protect from light.

Gelation may occur if the medicine is stored in a refrigerator. The product changes from a gel-like substance to a slightly viscous or liquid solution after 2 to a maximum of 4 hours at a controlled room temperature (15–25°C).

6.5 Nature and contents of the container

Vials made of Ph.Eur. type I glass with grey teflon-coated chlorobutyl rubber stoppers and aluminium caps, packed in a carton.

1 vial containing 5 ml
5 vials containing 5 ml
10 vials containing 5 ml
1 vial containing 25 ml
1 vial containing 50 ml
1 vial containing 100 ml

Glass bottle with/without transparent plastic container (ONKO safe).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Doxorubicin may be administered as an intravenous solution diluted to a concentration of 0.1 mg/ml to 1.0 mg/ml in 9 mg/ml (0.9%) sodium chloride solution for infusion or in 50 mg/ml (5%) glucose solution for infusion.

Handling and disposal specifications specified for cytostatic agents must be observed.

Caution is advised in the handling of doxorubicin. All contact with the solution should be avoided. Strict aseptic techniques should be followed during preparation; protective measures must include the use of protective gloves, protective masks, goggles and protective clothing. The use of a vertical laminar air flow (LAF) system is recommended.

Staff should be trained in the correct technique of handling cytostatic agents. Pregnant members of staff must not be allowed to work with these medicinal products.

If doxorubicin comes into contact with the skin or mucous membranes, the exposed area must be washed thoroughly with soap and water. If the substance comes into contact with the eyes, they should be rinsed with water or with sterile physiological saline solution, and an ophthalmologist should be consulted.

Vials and injection material, including gloves, must be destroyed in keeping with the standard medical procedure for the disposal of cytostatic agents. Unused medicinal product and waste material should be disposed of according to national regulations.

Any spilled or leaked doxorubicin should be treated with diluted sodium hypochlorite solution (1% available chlorite), which is preferably left to work overnight and then flushed away with water.

All cleaning materials should be disposed of in the manner outlined above.

Vials should be at room temperature before being punctured with a needle.

Use is recommended only under the supervision of physicians experienced in cytostatic therapy due to the variety of existing dosage regimens.

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH, Kundl
Biochemiastrasse 10 6250
Austria

8. MARKETING AUTHORISATION NUMBER

Not applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable

10. DATE OF REVISION OF THE TEXT

08/2020

PRESCRIPTION ONLY/PHARMACY SALE ONLY

Prescription only, pharmacy sale only. No repeat dispensing