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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doxorubicin EBEWE 2 mg/ml concentrate for infusion solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of sterile concentrate contains 2 mg of doxorubicin hydrochloride.
Each 5 ml vial contains 10 mg of doxorubicin hydrochloride.
Each 25 ml vial contains 50 mg of doxorubicin hydrochloride.

Excipient with known effects: 1 ml of sterile concentrate contains 3.54 mg of sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for infusion solution.
Clear, blood-coloured liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Soft tissue or osteogenic sarcoma.
- Hodgkin disease and non-Hodgkin lymphoma.
- Acute lympho leukaemia, acute myeloleukaemia.
- Multiple myeloma.
- Thyroid, breast, ovarian, bladder, small cell lung, endometrial, uterine lining, cervical, stomach, pancreatic, prostate, testicular, and liver carcinoma.
- Neuroblastoma.
- Head, neck and Wilms tumour.
- Superficial bladder carcinoma, carcinoma *in situ*.

4.2 Posology and method of administration

The required dose of doxorubicin solution can either be injected over 2–5 minutes or infused into a system with 0.9% sodium chloride or 5% glucose injection solution or a mixture of sodium chloride and glucose injection solutions. When the prepared infusion solution is injected intravenously immediately, the peak concentration in the blood will be higher than when infused, potentially leading to more severe toxic effects on the heart.

Dosage

Elderly patients

Monotherapy
Dosage depends on the type of cancer, heart and liver function, and any concomitant chemotherapy medications.
When treated with doxorubicin alone, the usual recommended single dose is 60–75 mg/m^2 body surface area. It is administered intravenously every 3 weeks. It can be administered in two different ways: the full dose at once or 20 mg/m^2 body surface area for three consecutive days. An alternative dosage is to administer 20 mg/m^2 body surface area intravenously weekly.

The total maximum dose should not exceed 450–550 mg/m^2 body surface area.

It has been shown that weekly administration of doxorubicin is as effective as administration every 3 weeks, but with a lesser toxic effect on the heart. Although the recommended weekly dose is 20 mg/m^2 body surface area, objective responses have also been observed with a dose of 6–12 mg/m^2 body surface area.

Complex treatment
When used with other cytostatics with similar toxic effects, a lower dose of doxorubicin should be used.
Maximum total dose. If the patient has received radiation to the mediastinal area, has heart disease, or is concurrently treated with other cancer drugs that cause heart toxicity but are not from the anthracycline group, the total maximum recommended dose is 450 mg/m^2 body surface area.

Special populations

Patients with hepatic impairment
For patients with impaired liver function, the doxorubicin dose should be reduced. If the serum bilirubin level is elevated, treatment should be at a lower dose: if it is 12–30 mg, half the usual dose should be administered; if > 30 mg, a quarter of the usual dose should be given.

Patients with renal impairment
For patients with impaired kidney function, the dose usually does not need to be reduced.

For patients at risk of heart disorders
In patients with a higher risk of heart toxicity, the single dose of doxorubicin should be administered as a continuous 24-hour infusion rather than by bolus injection. This method reduces the incidence of cardiac toxicity without diminishing therapeutic effectiveness. For these patients, left ventricular ejection fraction must be measured before each infusion.
As the total dose increases, the risk of cardiomyopathy gradually rises. The total dose should not exceed 450–550 mg/m^2 body surface area.
For patients with heart disease or those who have received radiation therapy to the heart or mediastinal area, the total dose should not exceed 400 mg/m^2 body surface area (heart function must be closely monitored in these patients, see section 4.4).
When used with other cancer medications, the recommended dose of doxorubicin is 50–75 mg/m^2 body surface area. During combination therapy, due to the additive effect, there may be stronger suppression of myeloid tissue function.

Paediatric population
Children should be treated with a lower dose, as they have a higher risk of delayed heart toxicity, and their heart function should be monitored during treatment. There may be toxic effects on myeloid tissue, which are most pronounced 10–14 days after the administration of doxorubicin. After this, bone marrow function recovers quickly because children, compared to adults, have a larger bone marrow reserve.

Superficial bladder carcinoma, carcinoma in situ
A dose of 50 mg of doxorubicin, diluted in 50 ml of isotonic sodium chloride solution, should be instilled into the bladder using a sterile catheter. Initially, this dose should be instilled weekly, and later, monthly. The optimal duration of treatment has not been established. Treatment can take 6-12 months.
As very little doxorubicin is absorbed from the bladder into the systemic circulation, the maximum total dose restriction for intravenous administration does not apply.
When administering doxorubicin intravenously, care should be taken to avoid extravasation, as it may cause local tissue necrosis and thrombophlebitis.
Doxorubicin solution should not be administered subcutaneously, intramuscularly, into the subarachnoid space, or infused intravenously for extended periods.
When the doxorubicin solution is mixed with heparin or 5-fluorouracil, precipitation occurs, so it should not be mixed with any other medicinal products.

Method of administration
It can be administered intravenously or instilled into the bladder.

4.3 Contraindications

- Hypersensitivity to doxorubicin, other anthracyclines, anthraquinone derivatives, or any excipient listed in section 6.1.
- Pregnancy and lactation (see section 4.6).

Contraindications for intravenous administration
- Patients with significant bone marrow suppression (including those with an increased tendency to bleed).
- In the case of a history of cardiopathology (unstable angina, progressive heart failure, severe heart arrhythmias, conduction disturbances, acute inflammatory cardiopathy, myocardial infarction within the last 6 months, or cardiomyopathy).
- Patients with severe renal and hepatic impairment.
- Patients previously treated with an anthracycline (e.g., epirubicin, idarubicin, or daunorubicin) up to the respective maximum cumulative dose.
- Acute infectious diseases
- Concomitant use with live and live-attenuated vaccines (for yellow fever, varicella, shingles, measles, mumps, rubella, tuberculosis, rotavirus, influenza) or less than 6 months after vaccination (see sections 4.4 and 4.5).

Contraindications for intravesical administration:
- Invasive tumor that has penetrated the bladder wall.
- Urinary tract infection and bladder inflammation.
- Hematuria.

4.4 Special warnings and precautions for use

Before starting treatment with doxorubicin, any acute toxic effects from previous cytotoxic therapy (e.g., stomatitis, neutropenia, thrombocytopenia, systemic infectious disease) must have resolved.

Treatment with doxorubicin requires close monitoring of the patient and their laboratory test results. Liver and kidney function must be checked before and during treatment. (see section 4.2).

Serum uric acid levels should be monitored, and if hyperuricemia occurs, appropriate treatment must be initiated.

Appropriate measures should be taken to control potential systemic infections before starting treatment. Doxorubicin should only be administered by a safe intravenous injection method, as extravasation can cause local necrosis and thrombophlebitis.

In obese patients (> 130% of ideal body weight), doxorubicin clearance is reduced (see section 4.2).

Cardiac toxicity
The risk of toxic effects on the myocardium may be increased after concomitant or previous radiotherapy in the mediastinal/pericardial area or after treatment with other potentially cardiotoxic substances, as well as in patients with a clinical condition caused by specific diseases, such as anemia, leukemic pericarditis, and/or myocarditis.

Heart function must be carefully evaluated before starting treatment and closely monitored during treatment to minimise the risk of cardiotoxicity, which has also been identified for anthracyclines.

A history of heart disease and previous treatment with anthracyclines at high cumulative doses or treatment with other substances that can cause cardiotoxic effects are risk factors for increased cardiotoxicity from doxorubicin.

Children and adolescents are at higher risk for cardiotoxicity, particularly late-onset toxicity.

It has been shown that the risk is higher in female patients than in male patients. Cardiological monitoring is recommended to assess this effect.
Therefore, before starting treatment, the benefit-risk ratio of doxorubicin therapy should be considered for these patients.

Cardiotoxicity can manifest in two distinct forms:
The early type is dose-independent and characterised by nonspecific ECG changes (ST-T wave changes, sinus tachycardia, supraventricular and ventricular extrasystoles).
Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and His bundle branch block, have also been reported.
These symptoms typically do not indicate late cardiotoxicity and are clinically insignificant. In most cases, treatment can be continued.

The late type is dose-dependent and characterised by cumulative toxicity, presenting as cardiomyopathy. This reaction usually develops during the late period of the doxorubicin treatment course or within 2–3 months after the completion of therapy. However, such cases have been observed even later (several months or years after treatment).

It often manifests as left ventricular failure and/or signs of congestive heart failure (CHF), such as dyspnoea, pulmonary oedema, peripheral oedema, cardiomegaly, hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects, such as pericarditis or myocarditis, have also been observed. The most severe form of anthracycline-induced cardiomyopathy is life-threatening congestive heart failure (CHF), which represents the cumulative dose-limiting toxic effect of the drug.

Since there is no reliable method for predicting acute heart failure, anthracycline-induced cardiomyopathy may be associated with a prolonged decrease in the QRS complex amplitude, prolongation of the systolic time interval (PIP/LV-DSI) beyond normal limits, and a reduced left ventricular ejection fraction (LVEF) below baseline values prior to treatment.
Before and during treatment, ECG, echocardiography, multi-gated acquisition radionuclide ventriculography (MUGA), and LVEF should be monitored.

It is believed that early diagnosis of doxorubicin-induced myocardial damage is important for the benefit of pharmacological treatment. Treatment with digitalis glycosides, diuretics, salt restriction, and bed rest is recommended.

The risk of heart failure increases slowly as the cumulative dose increases from 300 mg/m^2 of body surface area, with a frequency of about 1–2%, and the risk increases sharply when the cumulative dose reaches 450–550 mg/m%². The risk of heart failure increases sharply with higher doses, therefore it is not recommended to exceed the maximum cumulative dose of 550 mg/m^2 body surface area.

Other risk factors for cardiotoxicity include active and latent cardiovascular diseases, prior or concurrent radiation therapy to the mediastinal and pericardial areas with radioactive rays, previous treatment with other anthracyclines or anthraquinones, concurrent use of medications that may impair heart contractility (e.g., trastuzumab), and age over 70 years. In such cases, the total cumulative dose should not exceed 400 mg/m^2 for adults. For patients receiving high cumulative doses and those with risk factors, heart function should be carefully monitored. However, doxorubicin can cause cardiotoxicity even at low cumulative doses, and even if risk factors were not anticipated.

It is likely that the toxic effects of doxorubicin and other anthracyclines or anthraquinones are cumulative.

Anthracyclines, including doxorubicin, should not be administered together with other cardiotoxic drugs unless the patient's heart function is closely monitored (see section 4.5).
Patients receiving anthracyclines after treatment with other cardiotoxic drugs, especially those with a long half-life, such as trastuzumab, are at a higher risk of developing cardiotoxicity. The half-life of trastuzumab is approximately 28–38 days, but it remains in the bloodstream for up to 27 weeks after treatment cessation. Therefore, anthracyclines should not be administered until 27 weeks after trastuzumab treatment ends. If anthracyclines are administered earlier than 27 weeks, careful monitoring of heart function is recommended.

Bone marrow function suppression
As with other cytotoxic agents, doxorubicin can suppress bone marrow function.

Blood tests, including a leukogram, should be performed before each treatment cycle and during treatment.
The most significant hematologic toxicity of doxorubicin, and the most common dose-limiting toxicity, is dose-dependent transient leukopenia and/or neutropenia.
Leukopenia and neutropenia (usually transient) are more severe with high-dose regimens, reaching their lowest point 10–14 days after treatment, with blood parameters typically normalizing by day 21.

Thrombocytopenia and anemia may also occur. Severe bone marrow suppression may lead to clinical consequences such as fever, infection, sepsis, septic shock, bleeding, tissue hypoxia, or death.

Rare reports of secondary leukemia (with or without a pre-leukemic phase) have been observed in patients treated with anthracyclines, including doxorubicin. Secondary leukaemia is more common when anthracyclines are used in combination with DNA-damaging anticancer agents or radiation therapy, or in patients previously treated with high doses of cytotoxic agents, or those receiving very high anthracycline doses. The latent period for such cases of leukaemia may range from 1 to 3 years.

Gastrointestinal disorders
Doxorubicin may cause vomiting. Mucositis or stomatitis typically develops shortly after the start of treatment and may progress to mucosal ulceration within a few days in severe cases. Most patients recover from this side effect by the third week of treatment.

Liver function
Doxorubicin is primarily eliminated through the bile. Before and during treatment with doxorubicin, total serum bilirubin levels should be measured. In patients with elevated bilirubin levels, clearance is typically reduced, and the risk of toxicity is increased. In such cases, it is recommended to reduce the dose (see section 4.2). Doxorubicin should not be used in patients with severe liver dysfunction. (see section 4.3).

Skin reactions at the injection site
After injection into a small vein or repeated injection into the same vein, venous sclerosis may occur. Strict adherence to the recommended administration method reduces the risk of phlebitis/thrombophlebitis at the injection site (see section 4.2).

During intravenous injection, doxorubicin extravasation (leakage near the vein) may cause local pain, severe tissue damage (blister formation, severe cellulitis), necrosis, and thrombophlebitis.
Sharp pain or burning around the infusion needle indicates extravasation. If extravasation occurs, the injection or infusion should be immediately stopped. The cannula should be left in place briefly to allow for quick aspiration.

It is recommended to infuse dexrazoxane intravenously within 6 hours of extravasation (for dosing and other information, refer to the dexrazoxane SPC). In cases where dexrazoxane is contraindicated, it is recommended to apply 99% DMSO (dimethyl sulfoxide) locally to an area twice the size of the affected area (4 drops per 10 cm^2 of skin surface) and repeat three times daily for 14 days. If necessary, tissue removal should be considered. Due to the contrasting mechanism, the area should be cooled, for

example, to reduce pain, in conjunction with DMSO application (vasoconstriction before vasodilation). Other methods in the scientific literature are controversial and of unclear value.

Other
Doxorubicin may enhance the toxic effects of other anticancer treatments. It may worsen cyclophosphamide-induced haemorrhagic cystitis and exacerbate the hepatic toxicity of 6-mercaptopurine.

Furthermore, doxorubicin has been reported to enhance the toxic myocardial, mucosal, skin, and liver reactions caused by radiation therapy with radioactive rays. In rare cases, thrombophlebitis, thromboembolic events, including pulmonary embolism (sometimes fatal), may occur.

Tumour degradation syndrome
Doxorubicin, due to extensive purine catabolism associated with rapid tumour cell breakdown (tumour lysis syndrome), may cause hyperuricemia. When starting treatment with doxorubicin, serum levels of uric acid, potassium, calcium, phosphorus, and creatinine should be monitored. Hydration, urinary alkalinisation, and prevention of hyperuricemia with allopurinol can reduce the potential complications of tumour lysis syndrome.

Additional warnings and precautions regarding other routes of administration

Intra-bladder administration
Intravesical administration of doxorubicin may cause symptoms of chemical cystitis (i.e., painful urination, increased urine volume, painful and difficult urination, haematuria, bladder discomfort, bladder wall necrosis) and bladder contraction.
Special caution is required in cases where there are conditions that complicate catheterisation (i.e., urethral obstruction caused by bladder tumour invasion).

Vaccination
In patients with impaired immune function following chemotherapy, including after the use of doxorubicin, administration of live or attenuated live vaccines may result in severe infections, which can be fatal. Patients treated with doxorubicin should not be vaccinated with live vaccines. (see sections 4.3 and 4.5). Inactivated and killed vaccines may be administered, but the effectiveness of such vaccines may be reduced.

Each millilitre of this medicinal product contains less than 1 mmol (23 mg) of sodium, meaning it is essentially sodium-free.
Not relevant.

4.5 Interaction with other medicinal products and other forms of interaction

Doxorubicin is a potent substrate for cytochrome P450 CYP3A4, CYP2D6, and P-glycoprotein (Pgp). Concomitant administration of CYP3A4, CYP2D6, and/or Pgp inhibitors (e.g., verapamil) may increase doxorubicin plasma concentration, thereby enhancing its clinical effect. Concomitant administration of CYP3A4 inducers (e.g., phenobarbital, phenytoin, St. John's Wort preparations) and Pgp inducers may decrease doxorubicin concentration.
Concomitant administration of cyclosporine with doxorubicin may increase the area under the concentration-time curve (AUC) of both doxorubicin and doxorubicinol, possibly due to reduced clearance of the parent drug and decreased doxorubicinol metabolism.
Literature sources indicate that co-administration of cyclosporine with doxorubicin results in severe and prolonged hematologic toxicity compared to doxorubicin monotherapy. There have also been reports of coma and seizure cases occurring when cyclosporine and doxorubicin are used together.
Doxorubicin is most commonly used in combination with other cytostatic agents. Myelotoxic, hepatotoxic effects, and toxic effects on the gastrointestinal tract may accumulate.

When used in combination with immunosuppressive agents (cyclosporine, everolimus, sirolimus, tacrolimus, temsirolimus), the immunosuppressive effects are potentiated, and the risk of lymphoproliferative diseases increases.

During combined treatment with other medicinal products that may cause cardiotoxic effects or when used with cardioactive drugs (e.g., calcium channel blockers), heart function should be closely monitored. Concurrent treatment that affects liver function may also alter doxorubicin metabolism, pharmacokinetics, and therapeutic and/or toxic effects.
Doxorubicin strongly suppresses bone marrow function. Therefore, during combined treatment with drugs that have similar effects, it is likely that the bone marrow suppressive effect will be enhanced. (see section 4.4).

When doxorubicin is used with cyclosporine, the metabolism and clearance of both substances may decrease, leading to an increase in blood concentration. When doxorubicin and cyclosporine are used together, dosage adjustments may be required.

On the one hand, cimetidine reduces the plasma clearance of doxorubicin, while doxorubicin increases the AUC.

Phenobarbital, on the other hand, reduces the plasma concentration of doxorubicin and may therefore decrease its effectiveness.

Doxorubicin enhances the effects of radiotherapy. Even when administered long after the completion of radiotherapy, severe symptoms may occur in irradiated areas.

Doxorubicin is a potent radiosensitiser, and the phenomenon known as the "radiation recall reaction" can be life-threatening. Any previous or concurrent radiotherapy, or subsequent radiation treatment, may enhance the toxic effects of doxorubicin on the heart or liver.

If cyclophosphamide is administered after doxorubicin treatment, the cardiotoxic effects may be intensified, and hemorrhagic cystitis may worsen.

Doxorubicin treatment may cause an increase in uric acid levels, which may require dosage adjustment of uric acid-lowering medications.

The absorption of antiepileptic drugs (e.g., carbamazepine, phenytoin, valproate) is reduced when taken with doxorubicin.

Doxorubicin may reduce the oral bioavailability of digoxin. Therefore, during doxorubicin treatment, regular monitoring of digoxin plasma concentration is necessary.

The use of live and live-attenuated vaccines (e.g., yellow fever, varicella, shingles, measles, mumps, rubella, tuberculosis, rotavirus, influenza) is contraindicated due to the risk of fatal generalised disease. Vaccination is contraindicated during treatment and for 6 months after chemotherapy cessation.

During treatment with doxorubicin hydrochloride, patients should also avoid contact with individuals recently vaccinated with the live poliomyelitis vaccine.

Doxorubicin binds to heparin. This may cause precipitation and reduce the effectiveness of both medicinal products.

There may be an interaction with vitamin K antagonists, so more frequent monitoring of the international normalised ratio (INR) is recommended. INR).

The use of trastuzumab with anthracyclines (e.g., doxorubicin) is associated with a high risk of cardiotoxicity. Trastuzumab and anthracyclines should not be used in combination, unless in well-controlled clinical trials with monitored heart function.

Patients receiving anthracyclines after discontinuation of another cardiotoxic drug, especially one with a long half-life, such as trastuzumab, have an increased risk of cardiotoxicity. The half-life of trastuzumab is approximately 28–38 days, and the active substance remains in the bloodstream for up to 27 weeks. Therefore, the doctor should avoid prescribing anthracycline-based treatment for up to 27 weeks after trastuzumab discontinuation, if possible. If anthracyclines are used before this period, heart function should be closely monitored.

Amphotericin B administered during doxorubicin treatment can cause severe renal toxicity.

An increase in serum doxorubicin concentration has been reported when used with ritonavir.

When 400 mg of sorafenib is taken twice daily, the AUC of doxorubicin increased by 21–47%, but in some cases, the AUC remained unchanged. The clinical significance of these results is unknown.

Cases of necrotising colitis with severe infections have been reported with combined doxorubicin and cytarabine treatment.

Paclitaxel may increase the plasma concentration of doxorubicin and/or its metabolites when administered before doxorubicin. If doxorubicin is administered before paclitaxel, this effect is not significant.

4.6 Fertility, pregnancy and lactation

Fertility
In women, doxorubicin may cause amenorrhea and infertility during treatment. Ovulation and menstruation seem to return after the treatment is completed, although premature menopause may occur.
In animal studies, toxic effects of doxorubicin on male reproductive organs were observed (testicular atrophy, diffuse seminiferous tubule degeneration, and hypospermia).

Doxorubicin is mutagenic and may cause chromosomal damage in male spermatozoa. Induced oligospermia or azoospermia may be permanent. However, in some cases, sperm count normalised, which may occur several years after treatment completion. Men treated with doxorubicin should use effective contraception. Doxorubicin may cause irreversible infertility.

Before starting treatment, male patients should be informed about sperm preservation options.
Doxorubicin causes teratogenic and embryotoxic effects in rats.

Pregnancy and breastfeeding
Doxorubicin should not be used during pregnancy and breastfeeding.
Doxorubicin should not be used during pregnancy and lactation.
Due to the potential genotoxic effects of doxorubicin (see section 5.3), women of reproductive age should use effective contraception during Doxorubicin Ebewe treatment and for 7 months after treatment. Men are advised to use effective contraception and avoid fathering a child during Doxorubicin Ebewe treatment and for 4 months after treatment.
If parenthood is considered after treatment, genetic counselling is recommended.

4.7 Effect on the ability to drive and operate machines

The ability to drive and operate machinery may be impaired.

4.8 Undesirable effects

The following adverse reactions, reported during doxorubicin use, are listed according to MedDRA organ system classes and frequency. The following convention has been used for the classification of frequency: very common (≥ 1/10), common ≥ 1/100 to < 1/10), uncommon ≥ 1/1,000 to < 1/100), rare,

≥ 1/10,000 to < 1/1000), very rare, (< 1/10 000) and unknown (cannot be calculated from the available data).

Organ system group	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Frequency unknown**
Infections and infestations	Infections.	Sepsis/septicemia.	Septic shock.			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Acute lymphocytic leukaemia, acute myeloid leukaemia.			
Blood and lymphatic system disorders	Bone marrow function suppression, leukopenia, neutropenia, anaemia, thrombocytopenia, tissue hypoxia or necrosis, febrile neutropenia.		Secondary myeloid leukaemia.			
Immune system disorders				Angioneurotic oedema of the eyelids and tongue with respiratory deterioration.	Anaphylaxis.	Anaphylactic reaction.
Metabolism and nutrition disorders	Anorexia.	Dehydration.			Hyperuricemia	Tumour lysis syndrome (see section 4.4).
Eye disorders		Conjunctivitis.				Keratitis, lacrimation
Cardiac disorders		Toxic effects on the heart, such as cardiomyopathy, sinus tachycardia, tachyarrhythmia, bradycardia, congestive heart failure.			Atrioventricular block, His bundle branch block.	
Vascular disorders	Thrombophlebitis.	Phlebitis, bleeding.	Thromboembolism.		Shock.	Hot flashes.
Respiratory, thoracic and mediastinal disorders				Respiratory deterioration, nasal mucosal swelling, frequent breathing, shortness of breath,		

				radiation pneumonitis.		
Gastrointestinal disorders	Nausea/vomiting, mucositis, stomatitis, diarrheal.	Esophagitis, abdominal pain or burning sensation.	Gastrointestinal bleeding, colitis, erosive gastritis, necrotising colitis, erosive gastritis, necrotising colitis, sometimes with severe infections when doxorubicin is used together with cytarabine.		Erosions, change in oral mucosal color.	
Skin and subcutaneous tissue disorders	Local toxic effects, onycholysis, exanthema, erythema, photosensitivity, palmoplantar erythrodysesthesia syndrome, alopecia.	Pruritus, increased sensitivity of irradiated skin areas (“ирradiation recall reaction" syndrome), skin and nail hyperpigmentation, urticaria.			Redness of limbs.	
Musculoskeletal and connective tissue disorders					Generalised myasthenia.	Joint pain.
Renal and urinary tract disorders		Chemical cystitis following doxorubicin administration into the bladder (associated with dysuria, polyakuria, hematuria, polyuria, nocturia, stranguria, necrosis, bladder spasms).				Red-colored urine 1–2 days after drug administration, acute. Renal failure.
Reproductive system and breast disorders					Amenorrhea, oligospermia, azoospermia.	

General disorders and administration site conditions	Fever, astenia, shivers.	Infusion site reaction.			General disability/weakness.	Venous sclerosis (see section 4.4).
Tests	Asymptomatic reduction of left ventricular ejection fraction, ECG, abnormal transaminase activity, weight gain[a].					

[a] In early-stage breast cancer patients receiving adjuvant therapy with doxorubicin (NSABP B-15 trial).
Adverse effects associated with doxorubicin treatment are usually transient.

Reporting of suspected adverse reactions
It is important to report suspected adverse reactions observed after the registration of the medicinal product, as this allows continuous monitoring of the benefit-risk ratio of the medicinal product. Healthcare or pharmaceutical professionals should report any suspected adverse reactions by directly completing the reporting form online in the Service's Medicinal Products Information System https://vapris.vvkt.lt/vvkt-web/public/nrvSpecialist or by filling out the Health Care or Pharmaceutical Professional Suspected Adverse Reaction (SAR) Reporting Form, which is published https://www.vvkt.lt/index.php?1399030386, and sending it via email to NepageidaujamaR@vvkt.lt.

4.9 Overdose

A very high single dose causes heart failure (including angina, chest pain, and myocardial infarction), occurring within 24 hours after administration, signs of myeloid tissue function suppression (particularly leukopenia and thrombocytopenia), which is most pronounced between 10 and 14 days, and toxic effects on the digestive tract (primarily mucosal inflammation).
If heart failure occurs, doxorubicin administration should be discontinued.
In cases of significant bone marrow suppression, general measures such as blood transfusion, antibiotic therapy, and transfer to an aseptic ward may be required.
Doxorubicin cannot be removed by dialysis.
The specific antidote for doxorubicin is unknown.

Chronic poisoning, i.e., cumulative doses greater than 550 mg/m^2 of body surface area, increases the risk of cardiomyopathy and may lead to heart failure, which requires standard treatment. Late-onset heart failure may occur up to 6 months after overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group – cytotoxic antibiotics and related preparations, anthracyclines and related preparations, ATC code – L01D B01.

Doxorubicin has been shown to have anticancer effects in several animal models. It is also effective in treating humans. There is no consensus on how doxorubicin and other anthracyclines act on tumours. Three biochemical mechanisms are considered possible: intercalation into DNA, membrane binding, and metabolic activation through reduction.

A major reason for ineffectiveness of doxorubicin, and other anthracyclines, is the development of resistance. To prevent cells from becoming resistant to the drug, it is recommended to use calcium

channel blockers, such as verapamil, as the main site of action of doxorubicin, i.e., the "target," is the cell membrane. By blocking slow calcium current channels, verapamil may facilitate a greater amount of doxorubicin entering the cells.
Chang and colleagues (1989) demonstrated *in vitro* studies with three pancreatic cancer cell lines that verapamil enhances the cytotoxic effect of doxorubicin. These authors also investigated the potential impact of the main metabolite of doxorubicin, doxorubicinol (present in human blood plasma, on its cellular uptake and retention, but concluded that it does not affect the entry of doxorubicin into cells or its duration within them. However, it should be noted that some researchers (Sridhar et al., 1992) have found that treatment with doxorubicin and verapamil in animals is associated with severe toxic effects.

5.2 Pharmacokinetic properties

Absorbtion
Oral doxorubicin is not absorbed and does not cross the blood-brain barrier.
If liver function is impaired, the clearance of doxorubicin and its metabolites may be reduced.

Distribution
The intravenous clearance of doxorubicin in blood plasma is rapid (half-life is 10 minutes), and a significant amount of the drug binds to tissues. The terminal half-life is approximately 30 hours.

Biotransformation
Some doxorubicin is biotransformed, primarily into doxorubicinol, and to a lesser extent into aglycone, and conjugated with glucuronides and sulphates.

Elimination
The drug is mostly excreted via bile and feces. Approximately 10 % doses are eliminated renally. 50–85% of circulating doxorubicin binds to plasma proteins. The volume of distribution is 800 – 3500 l/m^2.

5.3 Preclinical safety data

The intravenous LD_{50} of doxorubicin for rats, mice, and rabbits is 12.6 mg/kg body weight, 9.4 mg/kg body weight, and 6 mg/kg body weight, respectively. In elderly and young rats, intravenous doses of doxorubicin (2.5 mg/kg body weight and 5 mg/kg body weight, respectively) reduced body weight and shortened survival duration. Study data suggest that the toxic effects are stronger in older rats.
Due to its interaction with DNA and its cytotoxic effects, doxorubicin causes mutagenic effects. *In vitro* studies with human lymphocytes have shown chromosomal damage, and it induced carcinogenic, teratogenic, and embryotoxic effects in animals. Mice and rats, when given intravenous or intraperitoneal doses less than 1 mg/kg body weight during days 7–13 of gestation, did not show teratogenic effects, but when given a higher dose, i.e., 2 mg/kg body weight, for a longer period intraperitoneally, some rat fetuses developed esophageal and intestinal atresia and cardiovascular anomalies. In pregnant rabbits, when 0.6 mg/kg body weight was administered intravenously, abortion occurred on days 16–18, but no developmental defects were observed. Rats injected with 1 mg/kg body weight or 1.5 mg/kg body weight during days 6–9 or 10–12 of pregnancy showed renal damage in their offspring during the postnatal period.
Microscopic examination revealed severe cardiomyopathy in the hearts of humans, and various changes were observed in the hearts of mice, rats, rabbits, dogs, and monkeys, induced artificially in these animals. The appearance and nature of heart changes in rats and rabbits resemble those seen in human hearts, though the cardiomyopathy in rats is induced at lower doses than in rabbits. The pathogenesis of these complications is difficult to study as numerous complex biochemical reactions occur in the heart in such cases.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

Hydrochloric acid (to adjust pH)
Sodium chloride
Water for injection

6.2 Incompatibilities

Doxorubicin should not be mixed with any alkaline solution as it may undergo hydrolysis, nor with heparin or 5-fluorouracil, as precipitates may form. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.
After opening: use immediately.
The shelf life of the prepared infusion solution is 24 hours. (see section 6.4).

6.4 Special storage conditions

Store in a refrigerator (2 °–8 °C).
The vial should be stored in the outer box to protect the drug from light.
The sterile concentrate should be drawn from the vial immediately before use. From a microbiological perspective, the prepared infusion solution should be administered immediately. If it is not used immediately, the storage conditions and duration are the responsibility of the prescribing physician. The shelf life of the infusion solution stored at 2°°–8°°C is no longer than 24 hours, except when the sterile concentrate is diluted under controlled and validated aseptic conditions.

6.5 Nature and contents of the container

The vial is made of amber glass (Type I), sealed with a teflon-coated chlorobutyl rubber stopper, and covered with a peel-off aluminium cap. The following packages are available:
- The box contains one 5 ml vial (10 mg doxorubicin hydrochloride) of sterile concentrate;
- the box contains one 25 ml vial (50 mg doxorubicin hydrochloride) of sterile concentrate.

The vial may be without or with a protective plastic sleeve (*"Onco-Safe"* and *"Sleeving"*).

Not all pack sizes may be available.

6.6 Special precautions for disposal and other handling

For single patient use only.
It is essential to follow the handling rules for cytotoxic drugs. Since the drug has toxic effects, the following safety working guidelines are recommended:
- personnel working with the drug must have good proficiency in such working methods;
- pregnant women should not work with this medicinal product;
- anyone working with doxorubicin must wear protective clothing: a lab coat, protective goggles, and disposable gloves and a mask;
- materials used to dilute, administer, or clean up after the drug, including gloves, should be discarded in high-risk waste disposal bags, which are incinerated at 700 °C.

If doxorubicin sterile concentrate or prepared infusion solution accidentally comes into contact with the skin or eyes, it must be immediately washed with a large amount of water, water and soap, or sodium bicarbonate solution, and medical attention should be sought.

If doxorubicin sterile concentrate or prepared infusion solution spills or accidentally leaks onto any surface, it should be moistened with a 1% sodium hypochlorite solution, and then, preferably after overnight, washed with water.

All materials used for cleaning must be disposed of as indicated above.

Recommended infusion solutions for diluting sterile concentrate are 0.9% sodium chloride infusion solution, 5% glucose infusion solution, or a mixture of sodium chloride and glucose infusion solutions (see section 4.2).
Since the methods of administration vary, doxorubicin should only be administered under the supervision of a physician experienced in the treatment with cytotoxic drugs.

7. MARKETING AUTHORISATION HOLDER

Sandoz d.d.
Verovškova 57
SI-1000 Ljubljana
Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

5 ml - LT/1/95/0631/001
25 ml - LT/1/95/0631/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration 4 October 1995
Date of last re-registration 12 January 2007

10. DATE OF TEXT REVIEW

08 August 2023.

Detailed information about this medicinal product is available on the website of the State Medicines Control Agency under the Ministry of Health of the Republic of Lithuania http://www.vvkt.lt